Adjunctive Corticosteroid Therapy for Tuberculosis: A Critical Reappraisal of the Literature

David P. Dooley, John L. Carpenter, and Steven Rademacher*

An extensive, although largely forgotten, literature addresses the utility of adjunctive corticosteroid therapy in the management of tuberculosis. Corticosteroid therapy probably improves neurological outcomes of, and decreases mortality due to, tuberculous meningitis of moderate severity. Although therapy for tuberculous pericarditis is simplified (with less need for operative intervention) by adjunctive corticosteroid administration and there are fewer deaths, the incidence of subsequent constriction is not changed. The signs and symptoms of typical reactivation tuberculosis pneumonia, tuberculous pleurisy, and probably primary tuberculous disease (with lymphadenopathy) seem to decrease rapidly with corticosteroid therapy, although no differences in final outcomes have been observed. Corticosteroid regimens used in most studies varied greatly in duration and dosage and generally caused significant side effects. Corticosteroids do not appear to diminish the efficacy of adequate antimycobacterial therapy. Adjunctive corticosteroid therapy appears to offer significant short-term but (other than for tuberculous meningitis and effusive pericarditis) minimal long-term benefit for patients with tuberculosis.

Despite the availability of effective chemotherapy for tuberculosis (TB), significant morbidity and mortality due to this disease continue to occur. While multiple factors complicate therapy for TB, slow or even paradoxical responses to effective antibiotics, especially in far-advanced disease, have long hampered clinical efforts [1, 2]. As better antimycobacterial agents became available and clinical responses became more certain, the often tardy pace of clinical improvement continued to frustrate both patients and physicians. More efficiently bactericidal agents—such as isoniazid—may actually cause more profound acute neurological deterioration in patients with meningeal TB (with more pronounced brain swelling), presumably attendant to more rapid organism killing [3].

Local signs and symptoms of TB are at least partially caused by the host’s inflammatory response to the presence of the Mycobacterium tuberculosis bacillus [4]. It is probable that the systemic wasting syndrome associated with progressive TB is also related to the host’s inflammatory response, as mediated through excessive cytokine production [5]. It is reasonable to postulate, therefore, that potent antiinflammatory agents such as corticosteroids, known to suppress a myriad of inflammatory responses, may prove effective as adjunctive therapy in the management of TB.

Similar considerations have prompted investigators to conduct a range of studies over the past 40 years into the utility of adjunctive corticosteroid usage in therapy for TB. A perusal of recent reviews of therapy for TB suggests that this older body of data, especially that addressing adjunctive use in pulmonary forms of the disease, has been largely ignored. We critically reviewed the published literature addressing corticosteroid usage in therapy for TB. Where the data were adequate to determine whether corticosteroids are useful or not for a particular tuberculous syndrome, we develop reasonable recommendations. Areas where inadequate data addressing corticosteroid therapy have been generated are also discussed, and the available data are presented.

Historical Background

Early investigations into the effect of corticosteroid administration on M. tuberculosis infection were performed by using animal models of TB. Corticosteroid administration markedly enhanced the virulence of M. tuberculosis in these studies, in which no specific antituberculous agent was employed [6, 7]. When antituberculous agents were developed, repeated studies suggested that the deleterious effects of corticosteroid administration on M. tuberculosis infection were, for the most part, abrogated when effective therapy (streptomycin or isoniazid) was coadministered [8] (reviewed in [9]).

By the 1950s, anecdotal experience with humans suggested parallels to the animal models: corticosteroid therapy for patients with TB, without antituberculous therapy, was perilous.
Methods

The English language medical literature was searched through a MEDLINE (National Library of Medicine) review (1966 to 1996) of pertinent index topics (tuberculosis, corticosteroids, and related words). References obtained both from these articles and from book chapters were screened to compile a comprehensive collection of pertinent primary literature.

For a study to be accepted for scrutiny in the following sections, both a study group (using adjunctive corticosteroid therapy) and a control group (no use of corticosteroid therapy) had to be defined, the comparability of the groups had to be addressed, adequate antituberculous therapy must have been administered, and a defined course of corticosteroid therapy must have been employed. The use of what would now be considered suboptimal antituberculous therapy in earlier trials did not disqualify a study for scrutiny if both study and control groups received the same regimen, since an analysis of the utility of steroids can still probably be performed. Most studies were blinded, but many had nonblinded aspects (e.g., blinded radiographic readings in a nonblinded study). We elected to present only the “harder” endpoints in these studies (such as time to negativity of sputum culture, or death), i.e., endpoints for which it would have been difficult to introduce bias. The following data were recorded: the type of study, method of randomization (if used), number of patients, and antituberculous and corticosteroid regimens.

Side effects of corticosteroids were recorded, but many investigators did not document these effects as vigilantly as the intended beneficial effects. The few studies that attempted to accurately record side effects (e.g., [15]) reported them to be both frequent and occasionally severe. There is a strong suspicion, then, that side effects in other studies were grossly underreported. “Rebound” phenomenon, or the temporary flaring of symptoms, signs, or radiographically evident changes upon tapering or discontinuing corticosteroid therapy, was recorded, but, in general, this phenomenon was a minor problem and easily treated by the reintiation of corticosteroid therapy at low doses.

Outcomes were recorded and analyzed by the following: acute responses (the effect on local or systemic signs and symptoms within the first days, up to 2 weeks), long-term responses (including eventual fibrotic complications), mortality, and laboratory-defined responses (e.g., changes in CSF in patients with meningeal TB or the rate of conversion of sputum cultures to negative in cases of pulmonary TB). Few of the earlier studies included any formal analysis of their data. When adequate categorical data were reported, we performed statistical analysis (Fisher’s exact test; $P < .05$, statistical significance), the results of which are reported here. Several of the later studies included statistical analyses of their own data, the results of which are reported here.

Results

Pulmonary TB

Data from 11 randomized trials [15–26] that examined the effect of adjunctive corticosteroid therapy on pulmonary TB are presented in table 1. Although only four trials were double-blind, three other trials recorded radiographic responses in a blinded fashion, and all studies reported at least adequate matching of groups.

The first randomized, controlled trial to examine the effect of adjunctive corticosteroid therapy was from Scotland in 1957 [16]. Despite faster radiographic clearing in the corticosteroid recipients, no differences between the groups were seen in the rate of cavity closure or in the incidence of side effects of the antituberculous drugs. Transient and generally mild radiologically evident deterioration occurred in seven study patients (16%) following discontinuation of corticosteroid therapy.

In 1959, Weinstein and Koler [17] reported a randomized, double-blind investigation demonstrating that radiographically evident abnormalities cleared significantly faster in corticosteroid recipients. Bell et al. [15], in 1960, reported the results of a nonblinded study where the clinical symptoms in the most severely ill patients, in particular, assigned to the corticosteroid group abated significantly faster than did those in the severely ill control subjects (P < .01). However, these responses were determined by nonblinded observers. Extensive comparisons were made in this study of changes in sputum volume, sputum character, and rates of conversion of sputum cultures to negative, revealing no differences between groups.

The U.S. Public Health Service Tuberculosis Therapy trial, a multicenter study published in 1960 [18], is still the largest single investigation to address the question of the efficacy of steroids on TB. In nonblinded fashion, patients received either placebo or one of two prednisolone regimens (5 weeks vs. 9 weeks). Few beneficial or detrimental effects of the low dosages of prednisone used (20 mg/d at initiation) were seen in this trial. Although side effects were rare, there also appeared to be no protective effect from the allergic side effects of the antibiotics.

In an attempt to avoid eventual complications of steroid withdrawal, Angel et al. [19] treated study patients with adrenocorticotropic hormone (ACTH). While clinical symptoms and radiographically evident conditions abated faster in corticosteroid recipients, this study is significant in that it is the only investigation to describe a slower rate of conversion of sputum cultures to negative among steroid recipients (significant by 3 months, although comparable by 6 months). No clinically significant changes in pulmonary function tests (vital capacity,
Table 1. Summary of data on adjunctive corticosteroid therapy for pulmonary tuberculosis.

<table>
<thead>
<tr>
<th>Year(s)</th>
<th>Study design</th>
<th>No. of patients</th>
<th>Antibiotic regimen</th>
<th>Steroid regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>1957 [16]</td>
<td>Prospective, randomized</td>
<td>90 (44 steroid recipients)</td>
<td>INH, Stm, PAS</td>
<td>Prednisolone, 5 mg q.i.d. × 3 mo; ACTH, 30 U im × 2 successive d q2w</td>
</tr>
<tr>
<td>1959 [17]</td>
<td>Prospective, randomized, double-blind</td>
<td>100 (51 steroid recipients)</td>
<td>INH, PAS</td>
<td>Prednisolone, 5 mg q6h; tapered off by day 68</td>
</tr>
<tr>
<td>1960 [15]</td>
<td>Prospective, randomized, nonblinded</td>
<td>91 (45 steroid recipients)</td>
<td>INH, PAS, Stm × 3 mo, then INH and PAS</td>
<td>Prednisolone, 5 mg q.i.d. × 8 w; then tapered off over 2 w</td>
</tr>
<tr>
<td>1960 [18]</td>
<td>Prospective, randomized, double-blind</td>
<td>1,145 (381 placebo recipients, 383 9-w Prd recipients, 383 5-w Prd recipients)</td>
<td>INH and PAS × 32 w or Stm and PAS × 12 w, then INH and PAS</td>
<td>Prednisolone (5 w vs. 9 w), 20 mg/d × 3 d, 15 mg/d × 4 d, then 10 mg/d until tapered off in last week</td>
</tr>
<tr>
<td>1961 [19]</td>
<td>Prospective, randomized (CXR readings blinded)</td>
<td>104 (54 ACTH recipients)</td>
<td>INH, PAS, Stm</td>
<td>ACTH, 60 U × 4 d, 50 U × 4 d, 40 U × 3 w, then 30 U × 6 w, tapered off over 3 w (13 w total)</td>
</tr>
<tr>
<td>1961, 1963</td>
<td>Prospective, randomized, nonblinded (CXR readings blinded)</td>
<td>346 (119 controls, 111 ACTH recipients, 116 Prd recipients)</td>
<td>INH, PAS, Stm</td>
<td>ACTH, 60 U once, then 50 U/d for 1st w, 30 U/d for 10 w, then tapered off over 2 w; Prd 50 mg once, then 37.5 mg/d for 1st w, 30 mg/d × 10 w, then tapered off</td>
</tr>
<tr>
<td>1963 [20]</td>
<td>Prospective, randomized, double-blind</td>
<td>27 (10 steroid recipients)</td>
<td>INH, PAS</td>
<td>Prednisolone, 48 mg/d × 2 w, tapered off in 2 w</td>
</tr>
<tr>
<td>1963 [21]</td>
<td>Prospective, randomized, non-blinded (CXR readings blinded)</td>
<td>100 (49 steroid recipients)</td>
<td>INH, PAS, Stm</td>
<td>Prednisolone, 40 mg/d, tapered to 20 mg/d until stable CXR findings, then tapered off; mean duration, 3 mo 16 d</td>
</tr>
<tr>
<td>1965 [22]</td>
<td>Prospective, randomized, double-blind</td>
<td>102 (52 steroid recipients)</td>
<td>INH, PAS</td>
<td>Methylprednisolone, 16 mg/d × 10 w, then tapered off over 2 w</td>
</tr>
<tr>
<td>1969 [25]</td>
<td>Prospective, randomized</td>
<td>104 (46 steroid recipients)</td>
<td>“Standard antituberculous drugs”</td>
<td>Prd, 40 mg q.o.d. × 6 w, then 25 mg q.o.d. for total of 6 mo</td>
</tr>
<tr>
<td>1983 [26]</td>
<td>Prospective, randomized, part of larger drug study</td>
<td>673 (334 steroid recipients)</td>
<td>Varied: INH, PZA, Stm × 5 or 7 mo with or without Rif × 2 mo</td>
<td>Prd, 60 mg/d 6 d a week, tapered off after 8 w</td>
</tr>
</tbody>
</table>

NOTE. ACTH = adrenocorticotropic hormone; CXR = chest roentgenogram; DLCO = diffusion capacity of carbon monoxide; INH = isoniazid; MMEFR = maximal midexpiratory flow rate; MVV = maximal voluntary ventilation; PAS = para-aminosalicylic acid; PFTs = pulmonary function tests; Prd = prednisone; PZA = pyrazinamide; q.o.d. = every other day; Rif = rifampin; Stm = streptomycin; × = for.

* Time to conversion of sputum culture to negative.
² Physiological, radiographic, or pulmonary functional parameters measured within days to <3 months of start of therapy.
³ Physiological, radiographic, or pulmonary function parameters measured after 3 months from start of therapy.

maximal midexpiratory flow rate, and maximal breathing capacity), analyzed for the first time in this study, were found. In 1961 and 1963, the Research Committee of the British Tuberculosis Association reported the results of a large trial of prednisone, ACTH, and placebo [20, 21]. Overall, clinical and radiographically evident improvement occurred faster in prednisone recipients than in controls, with intermediate findings for ACTH recipients. Slight but perceptible clinical “rebound” phenomena occurred in one-third of the prednisone recipients when therapy was completed. While ACTH was not as effective
### Table 1.  (Continued)

<table>
<thead>
<tr>
<th>Endpoints measured</th>
<th>Microbiology*</th>
<th>Acute¹</th>
<th>Chronic²</th>
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<tbody>
<tr>
<td>No difference in rate of sputum culture conversion</td>
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<td>Greater weight gain, faster CXR clearing in steroid group, significant at 1st and 2nd mo</td>
<td>No difference in CXR clearing or cavity closure by 6 mo</td>
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<tr>
<td></td>
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<td>Significantly better CXR clearing (especially advanced disease)</td>
<td>No difference in deaths or hospital stay; greater cavity closure in steroid group, but this group was operated on more often</td>
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<td>No difference in rate of sputum smear or culture conversion</td>
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<td>Rapid (1st mo) significant improvement in seriously ill patients’ conditions in steroid group; no difference in amount or character of sputum</td>
<td>No difference in CXR clearing or cavity closure at 3-mo follow-up</td>
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<td>Faster rate of sputum culture conversion in control group (significant at 3 mo); no difference at 6 mo</td>
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<td>Slightly faster CXR clearance in either Prd group compared with placebo group</td>
<td>Slight difference in CXR clearance persisted at 12-w follow-up</td>
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<td>No difference in rate of sputum culture conversion at 3 and 6 mo</td>
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<td>‘‘Clinical improvement’’ and weight gain faster in Prd group, followed by ACTH group, then control group; significantly better CXR clearance at 3 mo in Prd and ACTH groups</td>
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strated rapid early clinical and radiographically evident improvement in steroid recipients with eventual comparability of symptoms, radiographs, and pulmonary function tests (including measurements of flow, volume, oxygenation, and carbon monoxide diffusing capacity).

In a double-blind trial in 1965, Johnson et al. [24] demonstrated much faster clinical and radiographically evident improvement in the conditions of patients given low doses of corticosteroids for prolonged durations. These differences were particularly significant in advanced cases. Radiographically evident “rebound” phenomena occurred following completion of the steroid regimen in 60% of cases (especially in cases of advanced disease); symptoms of clinical “rebound” phenomena occurred briefly in one-half of cases. At least moderate abatement in cough and sputum production was more often seen in corticosteroid-treated patients (28 [61%] of 46) (P < .05). Unusually complete 5-year follow-up data were available in this study through the Veterans Administration system; these data revealed that control patients were more likely than corticosteroid recipients to have worsened or to have died of TB relapses or related respiratory illnesses (bronchitis, respiratory insufficiency, or pneumonia) (seven of 50 vs. one of 52, respectively; P < .025).

Malik and Martin [25] reexamined the effect of corticosteroid therapy on pulmonary function in 1969. Although abatement of symptoms and radiographically evident improvement were more pronounced in corticosteroid recipients, an effect on multiple pulmonary function parameters was not obvious (including the forced vital capacity, maximal expiratory flow rate, nitrogen washout, and resting and exercise blood gas levels determined at baseline, 6 months, and 12 months). The maximal voluntary ventilation in corticosteroid recipients was better at 6 months, but there was no difference between groups at 12 months. In contradistinction to Angel et al. [19], conversion of sputum cultures to negative was actually significantly faster (at 8 and 12 weeks) in the corticosteroid group.

While conducting a very large trial comparing short-course regimens (with or without rifampin) in Madras, India, the Indian Tuberculosis Research Centre [26] included a nonblinded randomization of patients with pulmonary TB to an 8-week prednisolone arm or a control arm. While little data on immediate clinical responses were given in this report, the study is significant in two ways. First, it is the only trial of adjunctive corticosteroid usage with short-course therapy, resulting in comparably low rates of relapse in steroid and control groups. Second, large numbers of patients from whom isolates of M. tuberculosis resistant to both isoniazid and streptomycin were recovered before the trial were entered into the study. These patients were then treated with two effective agents for only 2 months, and only one effective agent (pyrazinamide) was administered for the remainder of their courses. Analysis revealed that corticosteroid-treated patients responded less frequently to antibiotic therapy than did control patients, a result that recapitulated previous observations on adjunctive cortico-

steroid therapy when used with subadequate treatment regimens for animals [27, 28] or humans [9].

In summary, several controlled studies have suggested that the clinical conditions of patients with pulmonary TB treated with corticosteroids improve more rapidly overall than do those of control patients, an effect that may be more pronounced in patients with severe disease. The data suggest an absence of long-term beneficial effects of corticosteroid usage (in particular, on mortality or chronic restrictive disease). Other than rates of cavity closure, which do not seem to be affected by corticosteroid usage, faster radiologically evident responses are usually seen with the adjunctive use of corticosteroids. These radiographically evident improvements are of uncertain significance to the individual patient. A minority of patients may have mild “rebound” phenomena if corticosteroid therapy is discontinued too abruptly. When corticosteroids are given with adequate antituberculous therapy, the rate of clearance of M. tuberculosis from the sputum is not reduced, nor is the rate of long-term cure (even with short-course therapy). As expected, corticosteroid administration in the face of inadequate chemotherapy appears to be harmful to the patient.

Tuberculous Meningitis

The trials investigating the effects of corticosteroid therapy on meningeal TB suffer from differences in study design, corticosteroid regimens, and endpoints measured. In addition, not all patients included in these series were definitively proven to have tuberculous meningitis on the basis of a positive culture or a stain of a tissue biopsy specimen revealing granulomas with acid-fast bacilli. However, when the diagnosis was not culture or smear proven, the appropriate clinical picture, positive skin tests, and responses to directed antituberculous chemotherapy were generally present, and the inclusion of these patients in each of the following studies seems clinically reasonable.

Following an earlier positive but anecdotal experience with use of corticosteroids in the treatment of TB meningitis [29–31], a total of seven controlled trials, of varying degrees of rigor, were performed to examine this issue [32–38] (table 2). In a 1955 trial, Ashby and Grant [32] enrolled slightly sicker patients (according to Medical Research Council criteria [39]) in the corticosteroid group by using the peculiar randomization of sequential group assignment. No laboratory parameters were reported, although comment was made that CSF abnormalities and symptoms both abated much more quickly in corticosteroid recipients. No corticosteroid recipient, as compared with four of six control patients, had neurological sequelae (including one death) (P = .06, our statistical analysis).

Voljavec and Corpe [33] elaborately analyzed retrospective data for all 33 patients admitted to Battey State Hospital (Georgia) over a 6-year period for the treatment of moderate to severe tuberculous meningitis [39]. Although 11 other patients with early disease were not scrutinized, an important observation about these patients with early disease was recorded: all sur-
vived without sequelae, whether given steroids (three patients) or not (eight patients). The groups were comparable. While no laboratory or acute clinical parameters were studied, long-term survival was clearly greater in corticosteroid recipients. When all patients were stratified by severity of disease, those most ill did poorly with or without corticosteroid therapy; the greatest differential survival between groups was demonstrated for those patients with intermediate severity (and especially those with spinal block according to the authors’ definition) (one of 13 corticosteroid recipients died vs. six of 11 control patients; \( P < .025 \), our statistical analysis). This study was the first of two investigations [33, 34] to suggest that corticosteroid administration was not needed in mild disease and was not useful in very late disease.

The first randomized, double-blind trial to examine the effects of corticosteroids on meningeal TB was performed in 1963 [35]. Unfortunately, the randomization may have failed: one-half (nine of 18) of the controls were young children with poorer prognoses, while only three (16%) of 19 corticosteroid-treated patients had poorer prognoses. As expected, a greater survival was clearly greater in corticosteroid recipients. When all patients were stratified by severity of disease, those most ill did poorly with or without corticosteroid therapy; the greatest differential survival between groups was demonstrated for those patients with intermediate severity (and especially those with spinal block according to the authors’ definition) (one of 13 corticosteroid recipients died vs. six of 11 control patients; \( P < .025 \), our statistical analysis). This study was the first of two investigations [33, 34] to suggest that corticosteroid administration was not needed in mild disease and was not useful in very late disease.

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Table 2. Summary of data on adjunctive corticosteroid therapy for meningeval tuberculosis.

<table>
<thead>
<tr>
<th>Year [reference]</th>
<th>Study design</th>
<th>No. of patients</th>
<th>Antibiotic regimen</th>
<th>Steroid regimen</th>
<th>Microbiology/ laboratory*</th>
<th>Acute¹</th>
<th>Chronic¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>1955 [32]</td>
<td>Prospective sequential 6 patients admitted</td>
<td>12 (6 steroid recipients)</td>
<td>INH, Stm (im and IT)</td>
<td>Cortisone, 100 mg/d × months; then tapering with ACTH</td>
<td>CSF WBC count fell (^{&quot;\text{much more rapidly}) in steroid group</td>
<td>Recovery in 2–3 d in steroid group vs. 7–10 d in controls</td>
<td>0 of 6 steroid recipients had sequelae vs. 4 of 6 controls</td>
</tr>
<tr>
<td>1959 [33]</td>
<td>Retrospective, not randomized, comparable groups</td>
<td>33 (16 steroid recipients)</td>
<td>INH, Stm, PAS</td>
<td>Im cortisone followed by po Prd; mean duration, 34 d</td>
<td>Not done</td>
<td>Not mentioned</td>
<td>9 of 17 controls died vs. 3 of 16 steroid recipients</td>
</tr>
<tr>
<td>1963 [35]</td>
<td>Prospective randomized (control group more severely ill)</td>
<td>37 (19 steroid recipients)</td>
<td>INH, Stm, PAS</td>
<td>Hydrocortisone, 300 mg/d × 14 d; ACTH (&lt;50 U on days 11–14)</td>
<td>No difference in time to normal CSF glucose level, protein level, WBC count</td>
<td>Not mentioned</td>
<td>No difference in death or neurological sequelae</td>
</tr>
<tr>
<td>1969 [36]</td>
<td>Prospective randomized, double-blind</td>
<td>23 (11 steroid recipients)</td>
<td>INH, Stm</td>
<td>Dex, 9 mg/d, tapered off over 4 w</td>
<td>Glucose level, protein level, WBC count improved faster in steroid group; fewer herniations</td>
<td>Faster drop in CSF pressure by day 4 in steroid group</td>
<td>No significant difference in survival</td>
</tr>
<tr>
<td>1975 [37]</td>
<td>Prospective, randomized, double-blind</td>
<td>72 (36 steroid recipients)</td>
<td>INH, Stm, PAS</td>
<td>Prd, 1 or 10 mg/(kg·d), tapered off over 30 d</td>
<td>Not mentioned</td>
<td>Not mentioned</td>
<td>Greater survival in steroid group; no difference in sequelae</td>
</tr>
<tr>
<td>1983 [38]</td>
<td>Prospective, randomized</td>
<td>136 (66 steroid recipients)</td>
<td>INH, Stm, Eth</td>
<td>Dex, 8–12 mg/d × 3 w</td>
<td>Not mentioned</td>
<td>Not mentioned</td>
<td>No significant difference in survival or total ocular complications, but less optic atrophy in steroid group</td>
</tr>
<tr>
<td>1991 [34]</td>
<td>Prospective, randomized</td>
<td>160 (75 steroid recipients)</td>
<td>INH, Stm, Eth</td>
<td>Dex, 12 mg/d × adults, 8 mg/d × children, tapered off over 6 w</td>
<td>CSF glucose level, protein level, WBC count improved faster in steroid group</td>
<td>No difference in acute clinical resolution</td>
<td>More deaths, more sequelae in controls vs. steroid group</td>
</tr>
</tbody>
</table>

NOTE. ACTH = adrenocorticotropic hormone; Dex = dexamethasone; Eth = ethambutol; INH = isoniazid; IT = intrathecally; PAS = para-aminosalicylic acid; Prd = prednisone; Stm = streptomycin; \( 	imes \) = for.

* Resolution of CSF parameters.

¹ Physiological parameters measured within days to õ3 months of start of therapy.

¹ Physiological parameters measured after 3 months from start of therapy.
small. A significantly more rapid resolution of CSF parameters was seen in the corticosteroid group \( (P < .05) \) including the normalization of six of seven elevated CSF pressures compared with zero of five elevated CSF pressures in the control group by day 4 of therapy. Six of 12 control patients had a herniation syndrome compared with two of 11 corticosteroid recipients \( (P = NS, \text{our statistical analysis}) \). The investigators concluded that corticosteroids were useful for reducing cerebral edema but that the evident antiinflammatory effects were not useful in the reduction of long-term sequelae.

A more recent randomized, double-blind trial from Colombia used sequential analysis of matched pairs to evaluate the efficacy of corticosteroid therapy in the reduction of mortality due to tuberculous meningitis [37]. This analysis demonstrated that the corticosteroid group had a statistically significant advantage for short-term survival but that neurological sequelae in both groups at discharge appeared comparable. Long-term follow-up could not be done. The magnitude of the effect of corticosteroids could not be determined in this study, and no analysis of subsets to identify patient groups particularly amenable to corticosteroid therapy was presented.

Girgis et al. [38] performed a randomized study to determine the effects of corticosteroids on the appearance of ocular nerve abnormalities in patients with tuberculous meningitis. Despite a trend toward more severe neurological involvement in corticosteroid recipients, there was a nonsignificant trend toward longer survival in the corticosteroid group (especially in patients with mild and moderate [drowsy] neurological involvement [17 (68%) of 25 corticosteroid recipients survived vs. 22 (58%) of 38 control patients]) and a nonsignificant trend toward fewer ocular complications in the corticosteroid group (two of 27 survivors) than in the control group (seven of 28 survivors). While significantly more control patients than corticosteroid-treated patients had optic atrophy, these numbers were very small (four of 28 vs. zero of 27, respectively; \( P < .05 \)).

These investigators from Egypt subsequently performed the largest randomized (but nonblinded) study of the use of corticosteroid therapy for tuberculous meningitis [34]. Corticosteroid-treated patients for whom cultures were positive had less mortality than controls, whether all patients were considered (32 [43%] of 75 corticosteroid recipients died vs. 50 [59%] of 85 controls, respectively; \( P < .02 \)) or just those patients surviving \( \geq 10 \) days (seven [14%] of 50 corticosteroid recipients died vs. 17 [33%] of 52 controls, respectively; \( P < .02 \)). No difference was seen when patients who were admitted in comas were considered, but the survival of those patients who were drowsy at the time of admission was greater in the corticosteroid group than in the control group (23 [85%] of 27 vs. 21 [60%] of 35, respectively; \( P < .02 \)). Too few patients with minimal disease were admitted to be evaluated. While neurological complications (such as hemiparesis or hydrocephalus) were seen at the time of admission with comparable frequencies in both groups, fewer new complications occurred after admission in the corticosteroid group than in the control group (four [9%] of 43 vs. 10 [29%] of 35, respectively; \( P < .02 \)), and fewer deficits persisted at 2-year follow-ups in the corticosteroid group than in the control group (six [14%] of 43 vs. 13 [37%] of 35, respectively; \( P < .02 \)). CSF parameters (WBC count, glucose level, and protein level) normalized faster in the corticosteroid group \( (P < .04 \text{for each parameter}) \).

In summary, seven trials of various degrees of rigor have investigated the effects of corticosteroids on tuberculous meningitis. Five of these trials, including the largest and best analyzed study [34], demonstrated an advantage of adjunctive corticosteroid therapy over standard therapy for survival, frequency of sequelae, or both. When examined, CSF abnormalities and elevated CSF pressures resolved significantly faster in corticosteroid recipients. Both studies that stratified illness by severity at presentation [33, 34] noted the lack of effect of corticosteroids on either early disease or late disease (coma), but a significant benefit for patients with intermediate disease (drowsiness, single cranial nerve paresis, or hemiparesis). Three studies with shorter CS regimens (2–4 weeks) [35, 36, 38] demonstrated disappointing results; those studies with longer regimens (4 weeks to “months”) [32–34, 37] demonstrated significant beneficial effects. A regimen of dexamethasone at 8–12 mg/d [34, 38], or a prednisone equivalent [37], seemed as effective as, and had fewer side effects than, higher doses [37]. The use of corticosteroids to alleviate elevated intracranial pressure seemed to be accepted even by the authors of negative studies [36].

### Tuberculous Pericarditis

The efficacy of corticosteroid therapy for tuberculous pericarditis may differ for the different physiological stages of the disease (effusive, effusive-constrictive, and constrictive), but too often reports do not classify patients by these stages. In addition, constriction is a late complication of the effusive or effusive-constrictive stage, but patients in many investigations have not been followed up long enough to detect its development.

Even the best of the retrospective studies examining this question [40, 41] are characterized by the absence of group comparisons and poorly defined endpoints. An exception is the study by Rooney et al. [42] in which data on 28 patients were collected (table 3). Eighteen patients received corticosteroid therapy in addition to antituberculous therapy in a nonrandomized but well-matched manner. Patients treated with corticosteroids had a more rapid decrease in their pericardial effusion than did controls (5 vs. 12 weeks for the heart size to return to normal, respectively; no test for significance applied). Four patients in each group required pericardiectomy, presumably for control of reaccumulation of fluid. The conditions of 14 of 18 patients in the corticosteroid group improved without surgery compared with four of 10 patients in the control group \( (P = NS, \text{our statistical analysis}) \). Four of 10 control patients died, whereas none of 18 in the corticosteroid group died.
Table 3. Summary of data on adjunctive corticosteroid therapy for tuberculous pericarditis.

<table>
<thead>
<tr>
<th>Type of pericarditis, year [reference]</th>
<th>Study design</th>
<th>No. of patients</th>
<th>Antibiotic regimen</th>
<th>Steroid regimen</th>
<th>Microbiology*</th>
<th>Endpoints measured</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effusive constrictive 1987 [44]</td>
<td>Prospective, double-blind, randomized</td>
<td>114 (53 steroid recipients)</td>
<td>INH, Rif, Stm, PZA</td>
<td>Prd, 60 mg/d, tapered over 11 w</td>
<td>Not done</td>
<td>Faster improvement (pulse rate, JVP level, activity) in steroid group</td>
</tr>
<tr>
<td>Acute effusive 1970 [42]</td>
<td>Retrospective, not randomized</td>
<td>28 (18 steroid recipients)</td>
<td>INH, PAS, Stm</td>
<td>Prd, 80 mg/d, tapered over 6–8 w</td>
<td>Not done</td>
<td>Faster return to normal size heart in steroid group; 4 of 10 deaths without steroids vs. 0 of 18 deaths with steroids</td>
</tr>
<tr>
<td>1988 [43]</td>
<td>Prospective, double-blind, randomized</td>
<td>150 (76 steroid recipients)</td>
<td>INH, Rif, Stm, PZA</td>
<td>Prd, 60 mg/d, tapered off over 11 w</td>
<td>Not done</td>
<td>Fewer Prd recipients required repeated drainage; No difference in constriction; fewer deaths in Prd group</td>
</tr>
</tbody>
</table>

NOTE. INH = isoniazid; JVP = jugular venous pulse; PAS = para-aminosalicylic acid; Prd = prednisone; PZA = pyrazinamide; Rif = rifampin; Stm = streptomycin.
* Time to conversion of culture to negative.
† Physiological, radiographic, or cardiac functional parameters measured within days to ≤3 months of start of therapy.
‡ Physiological, radiographic, or cardiac functional parameters measured after 3 months from start of therapy.

(P < .01, our statistical analysis). Too few patients progressed to late constriction to discern differences in this parameter between groups.

Strang et al. [43] performed the only prospective, randomized, double-blind study investigating the utility of corticosteroid therapy for effusive pericarditis. Corticosteroid therapy significantly reduced the need for repeated pericardiocentesis for control of fluid accumulation (seven of 76 corticosteroid recipients vs. 17 of 74 controls; P < .05) and reduced the risk of death due to pericarditis (two of 76 corticosteroid recipients vs. 10 of 74 controls; P < .05). Three corticosteroid recipients compared with seven control patients required emergent pericardiectomy to prevent the development of cardiac tamponade (P = NS). There was no difference in the incidence of progression to constriction between the two groups.

Strang et al. [44] also performed a similar quality study of patients in the later effusive-constrictive phase of tuberculous pericarditis. By the recorded results of physical examination, electrocardiograms, and echocardiographic criteria, it is difficult to determine the extent to which constriction had already occurred in these patients. Nonsignificant differences were apparent between corticosteroid recipients and controls for death due to pericarditis (two of 53 vs. seven of 61, respectively) and for the need for pericardiectomy to prevent reaccumulation of fluid or acute cardiac decompensation (11 of 53 vs. 18 of 61, respectively). Faster resolution of signs of effusion, as evidenced by time to low pulse rate (P < .001) or the time to low jugular venous pressure (<5 cm; P < .05) or unrestricted physical activity (P < .05), was seen in patients in the corticosteroid group. However, there was no difference between the two groups in the development of constrictive pericarditis.

In summary, the use of corticosteroid therapy for acute effusive tuberculous pericarditis appears to decrease the amount of effusion and the reaccumulation of fluid. Therefore, fewer invasive measures are needed to control fluid accumulation. Overall mortality is decreased with the use of corticosteroids in this setting, probably secondary to the control of hemodynamically threatening effusion. Although corticosteroid use in the later effusive-constrictive stage seems to speed symptomatic and hemodynamic recovery, it does not significantly reduce the risk of death. The progression from any stage to chronic constrictive pericarditis does not seem to be inhibited by corticosteroid use.

Tuberculous Pleuritis

Ten trials of various degrees of experimental rigor that addressed steroid therapy for tuberculous pleural effusions have been published. Six studies are included here for analysis [45–50] (table 4); four studies, although controlled and carefully performed, cannot be evaluated because a comparison of groups was not presented [51–54].

Three problems cloud the interpretation of the data from these trials. First, pleural effusions complicate several different
**Table 4. Summary of data on adjunctive corticosteroid therapy for tuberculous pleural effusions.**

<table>
<thead>
<tr>
<th>Year [reference]</th>
<th>Study design</th>
<th>No. of patients</th>
<th>Antibiotic regimen</th>
<th>Steroid regimen</th>
<th>Microbiology*</th>
<th>Acute²</th>
<th>Chronic³</th>
</tr>
</thead>
<tbody>
<tr>
<td>1958 [45]</td>
<td>Historical and concurrent accidental controls, then prospective steroid arm</td>
<td>30 (16 steroid recipients)</td>
<td>INH, Stm</td>
<td>ACTH, 40 U/d (8 patients); cortisone, 7 dose (2 patients); Prd, 20 mg/d (4 patients), all × 8–12 w</td>
<td>Not mentioned</td>
<td>Mean time to resolution: 28 d, with 1 loculation, in steroid group compared with 60 d, with 6 loculations, in controls</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>1960 [46]</td>
<td>Prospective, randomized</td>
<td>50 (25 steroid recipients)</td>
<td>INH, Stm</td>
<td>Hydrocortisone intrapleurally, 250 mg × 1st 10 patients, 125 mg × last 15 patients; tap repeated q2w if fluid persisted, and hydrocortisone injection repeated</td>
<td>Not mentioned</td>
<td>Much faster defervescence in steroid group (1–2 d compared with 2–4 w in controls); loss of “toxemia” in 1–4 d in steroid group compared with 10–47 d in controls; significantly faster, more frequent absorption in steroid group</td>
<td>Less pleural thickening at costophrenic angles (numbers indeterminate) at 6- to 12-mo follow-ups</td>
</tr>
<tr>
<td>1960 [47]</td>
<td>Prospective, randomized</td>
<td>39 (20 steroid recipients)</td>
<td>INH, Stm (× 8 w)</td>
<td>Prednisolone, 10 mg t.i.d. × 2 d, then 4 mg t.i.d. to finish 8 w</td>
<td>Not mentioned</td>
<td>Much faster resolution of effusion in steroid group (1–2 w compared with &gt;6 w in controls); more often complete resolution at 4 and 8 w</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>1964 [48]</td>
<td>Not randomized, controlled</td>
<td>49 (12 patients with therapeutic aspirates only; 12 intrapleural hydrocortisone or Dex recipients; 25 oral prednisolone recipients)</td>
<td>INH, Stm × 6 w, then INH, PAS</td>
<td>Intrapleural steroids: hydrocortisone, 25 mg, or Dex, 8 mg q4d; prednisolone, 5 mg t.i.d. × 2–4 w, tapered off over next 2–4 w</td>
<td>Not mentioned</td>
<td>Much faster/more complete absorption of fluid in steroid groups than in controls; fewer aspirations required</td>
<td>Much less residual pleural thickening in oral steroid group</td>
</tr>
<tr>
<td>1964 [49]</td>
<td>Controlled, but unknown randomization</td>
<td>66 (28 steroid recipients)</td>
<td>INH, PAS, Stm</td>
<td>Triamcinolone, 20 mg/d, tapered q5d to off (30 d total); ACTH, 20 U for 2 d at end of therapy; hydrocortisone, 125 mg intrapleurally at start of therapy</td>
<td>Not mentioned</td>
<td>Rapid defervescence in steroid group; pleural fluid absorption equal for large effusions; significantly faster for small effusions (3.3 w in steroid group vs. 7 w in controls)</td>
<td>Greater residual thickening in control group at 12 mo by CXR (fair/poor result, 30% of controls vs. 0 of steroid group)</td>
</tr>
<tr>
<td>1988 [50]</td>
<td>Prospective, randomized, double-blind</td>
<td>40 (21 steroid recipients)</td>
<td>INH, Rif, Eth</td>
<td>Prednisolone, 0.75 mg/ (kg·d), tapered gradually per clinical response</td>
<td>Not mentioned</td>
<td>Fever, chest pain, dyspnea gone in mean of 2.4 d in steroid group vs. 9.2 d in controls; time to clear costophrenic angle, 54 d in steroid group vs. 123 d in controls</td>
<td>Pleural adhesions in 1 steroid recipient and 3 controls</td>
</tr>
</tbody>
</table>

**NOTE.** ACTH = adrenocorticotropic hormone; CXR = chest roentgenogram; Dex = dexamethasone; Eth = ethambutol; INH = isoniazid; PAS = para-aminosalicylic acid; Prd = prednisone; Rif = rifampin; Stm = streptomycin; 7 = unknown; × = for.

* Time to conversion of culture to negative.

1 Physiological, radiographic, or pulmonary functional parameters measured within days to <3 months of start of therapy.

1 Physiological, radiographic, or pulmonary function parameters measured after 3 months from start of therapy.
TB syndromes (the usual postprimary disease and occasionally chronic reactivation and miliary disease [55–57]). It is unclear whether acute complications (pain, fever, and dyspnea) or chronic local complications (restriction) occur with similar frequency in all groups, yet no group classifications are presented in these studies. Second, cases are usually diagnosed clinically, without confirmatory cultures; although most cases would be accepted by standard criteria, incorrectly diagnosed cases would confound results. Last, though the main chronic complication of tuberculous pleurisy is fibrosis with restrictive lung disease, this endpoint was scrutinized only once in a noninterpretable study [52]. In the other studies, the usual long-term follow-up was the radiographic determination of the presence or absence of pleural reactions, by themselves of uncertain significance to the patient.

The first trial to address this issue appeared in 1958 [45]; this study included 14 controls (13 consecutive patients “just before” the start of corticosteroid therapy and one later patient with a corticosteroid contraindication) and 16 study patients (the next 16 patients who received various steroid regimens for 2–3 months). Although the resolution of effusion volumes was remarkably faster in corticosteroid-treated patients than in the controls, no other endpoints were recorded.

Mathur et al. [46] in 1960 used the interesting approach of local instillation of hydrocortisone into involved pleural spaces (in the absence of other systemic steroid therapy). Acute toxicities were markedly reduced in the steroid group than in the controls, as were the amounts of effusion (resolution within 15 days: 18 [72%] of 25 vs. zero of 25, respectively; \( P < .0001 \), our statistical analysis). Long-term comparisons (limited to pleural thickening) were poorly defined. In the same year, Fleishman et al. [47] conducted a randomized trial of the treatment of pleural effusions in South African mine laborers. Antituberculous drugs–treated patients had slow resolution of effusion (four [21%] of 19 had resolution within 8 weeks), although faster resolution was seen in patients treated with both antituberculous drugs and corticosteroids (12 [60%] of 20; \( P = .02 \), our statistical analysis). Significantly faster “overall improvement” (the resolution of fever, pain, and malaise) was seen in the corticosteroid-treated patients as well. This trial lasted only 8 weeks.

Menon [48] reported the effect of steroid administration on a series of patients with considerable morbidity (43 of 49 consecutive patients had effusions at the third rib or higher). Different corticosteroid regimens were given, and the trial was not randomized, with patients with more serious disease (larger pleural effusions) deliberately assigned to the steroid groups. Resolution of pleural effusions was significantly faster in steroid-treated patients than in controls (resolution by 4 weeks: 29 [78%] of 37 vs. one [8%] of 12, respectively; \( P < .0001 \), our statistical analysis). Months after use, resolution of residual pleural thickening was significantly better in the oral steroid group than in the control group (no residual pleural scar at long-term follow-up: 23 [92%] of 25 vs. seven [58%] of 12, respectively; \( P < .25 \), our statistical analysis), with intermediate results for the intrapleural instillation group.

At the University of Helsinki, 66 patients were enrolled in a nonrandomized study [49] in which 28 were assigned to treatment with tapering doses of triamcinolone (without thoracentesis) and 28 received serial therapeutic thoracenteses. Despite the lack of therapeutic drainage, large effusions resolved as fast in corticosteroid recipients as in control (thoracentesis) patients; small effusions resolved significantly faster. At 6 and 12 months, significantly more patients in the corticosteroid group had “good” radiographic results; whether these differences were clinically significant for the patients was not addressed.

The only randomized, prospective, double-blind study addressing this question appeared in 1988 [50]. The steroid regimen was not straightforward, being tapered according to radiographic markers (e.g., tapered “by \( 1/2 \)” for effusions that had almost resolved), and the average tapering occurred over 2–3 months. The grouped symptom complex of “fever, chest pain, and dyspnea” resolved much faster in corticosteroid recipients than in controls (2.4 days vs. 9.2 days, respectively; \( P < .05 \)). Radiographically evident pleural effusions also resolved much faster in corticosteroid recipients than in controls (mean duration: 55 days vs. 123 days, respectively; \( P < .01 \)).

In summary, several studies have demonstrated beneficial effects of adjunctive steroid use with antituberculous chemotherapy for pleural effusions. The most recent study, of good design, supported the positive findings from earlier nonblinded studies. The most salutary effects appeared to be on acute symptoms (usually defined as pain, fever, and dyspnea). The current data suggest that corticosteroids possess no clinically significant efficacy for the prevention of the chronic endpoint of fibrosis (with consequent restrictive lung disease). All studies suggested a diminution of radiographically determined persistent scarring in corticosteroid-treated patients, but clinical correlations were lacking. Regimens varied from prednisone equivalent dosages of 20–40 mg/d for 4–8 weeks, with no evidence that higher doses or longer courses were more effective. Systemic corticosteroid therapy seemed more effective than local instillation in the two studies in which this question was investigated.

Primary TB

Two controlled studies of classic pediatric primary disease have addressed the utility of steroid use in the control of mediastinal lymphadenopathy associated with primary TB (table 5). In a small study, Keidan and Todd [58] randomized alternate admissions to adjunctive triamcinolone for 10 weeks. Endpoints were blinded radiographic readings; moderate or marked improvement in adenopathy by 1 month of therapy occurred in all eight corticosteroid-treated patients compared with no improvement in all seven control patients (\( P = .0002 \), our statistical analysis). Symptomatic endpoints were not reported.
Table 5. Summary of data on adjunctive corticosteroid therapy for primary tuberculosis.

<table>
<thead>
<tr>
<th>Year [reference]</th>
<th>Study design</th>
<th>No. of patients</th>
<th>Antibiotic regimen</th>
<th>Steroid regimen</th>
<th>Endpoints measured</th>
</tr>
</thead>
<tbody>
<tr>
<td>1961 [58]</td>
<td>Prospective, randomized</td>
<td>15 (8 steroid</td>
<td>INH, Stm,</td>
<td>Triamcinolone, 0.25 mg/(lb · d) × 4 w,</td>
<td>Microbiology*</td>
</tr>
<tr>
<td></td>
<td>(CXR findings blinded)</td>
<td>recipients)</td>
<td>both × 12 w</td>
<td>then 0.125 mg/(lb · d) × 4 w, tapered</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>off over next 2 w</td>
<td></td>
</tr>
<tr>
<td>1963 [59]</td>
<td>Prospective, randomized,</td>
<td>117 (58 steroid</td>
<td>INH, PAS</td>
<td>Pred (starting 2 w after antibiotics),</td>
<td>Acute²</td>
</tr>
<tr>
<td></td>
<td>double-blind</td>
<td>recipients)</td>
<td></td>
<td>5 mg/(kg · d), tapered to 1 mg/(kg · d)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>× 1 w, 1 mg/(kg · d) × 3 w, then</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>tapered off over 2 w</td>
<td></td>
</tr>
</tbody>
</table>

NOTE. CXR = chest roentgenogram; INH = isoniazid; PAS = para-aminosalicylic acid; Pred = prednisone; Stm = streptomycin; × = for.
* Time to conversion of culture to negative.
² Physiological, radiographic, or bronchoscopic parameters measured within days to <3 months of start of therapy.
³ Physiological, radiographic, or bronchoscopic parameters measured after 3 months from start of therapy.

In a large, double-blind trial in 1963, Nemir et al. [59] studied the effect of very high initial doses of prednisone (tapering over 6 weeks) on the bronchoscopic endpoint of size of endobronchial extension of lymphadenopathy (determined 4 weeks after steroid therapy was discontinued). The conditions of 39 (67%) of 58 corticosteroid-treated patients improved compared with 27 (46%) of 59 control patients (P < .05). Neither acute nor chronic symptoms were investigated. Side effects were carefully monitored and were distressingly common. Both of these studies showed no difference in the clearing of positive cultures between groups.

In summary, it appears that steroids are effective in rapidly reducing mass effects from mediastinal lymphadenopathy in patients with primary TB and may therefore decrease local obstructive complications (although this latter issue was not specifically addressed in the studies). Lower doses may be as effective as very high doses. Long-term follow-up, for evaluating relapses or the evolution of stenotic or ectatic segments, was not reported in these studies.

Endobronchial TB

Adjunctive corticosteroids have been used to treat endobronchial TB in an attempt to reduce eventual bronchial stenosis; no data on efficacy from controlled trials exist (other than those on the childhood subset of lymphatic extension into the bronchial lumen [58, 59]), and even anecdotes are not impressive [60]. A rare syndrome of endobronchial TB (presenting many weeks after the initiation of antituberculous therapy as nonresolving luminal granulomatous disease) may reflect hypersensitivity to the organism and anecdotally seems responsive to corticosteroid administration [61, 62].

Tuberculous Lymphadenitis

An adjunct to antituberculous therapy for peripheral lymphadenitis is needed, in that as many as one-third of involved node groups “flare” with an exacerbation of pain and swelling following the initiation of chemotherapy [63]. Unfortunately, despite comment that oral steroids may be useful in this setting [64], no controlled study has addressed the issue, and one is left with extrapolations from the data on mediastinal lymphadenopathy (see above [58, 59]).

Miliary TB

The only study of miliary TB that described patient characteristics sufficiently to allow a comparison of control and corticosteroid groups was reported from China in 1981 [65] (table 6). Nine (33%) of 27 corticosteroid recipients compared with five (18%) of 28 controls had meningeal involvement, possibly skewing the results in favor of the control group; the randomization method was unclear. Data on mortality showed a non-significant trend toward better outcome for the steroid group than for controls (death: two of 27 vs. five of 28, respectively). A more recent retrospective study that included an analysis of the effect of steroids on mortality in childhood miliary TB is
Table 6. Summary of data on adjunctive corticosteroid therapy for miliary tuberculosis.

<table>
<thead>
<tr>
<th>Year [reference]</th>
<th>Study design</th>
<th>No. of patients</th>
<th>Antibiotic regimen</th>
<th>Steroid regimen</th>
<th>Endpoints measured</th>
</tr>
</thead>
<tbody>
<tr>
<td>1981 [65]</td>
<td>Randomized</td>
<td>55 (27 steroid recipients)</td>
<td>INH, Stm, PAS × 6 mo, then INH and PAS to complete 2 y</td>
<td>Prd, 10 mg q.i.d. × 1 w (20 mg/d if mild symptoms, no meningitis), 20 mg/d × 6 w, then tapered by symptoms (variable total, 3–5 mo)</td>
<td>Not mentioned</td>
</tr>
</tbody>
</table>

NOTE. INH = isoniazid; NS = not significant; PAS = para-aminosalicylic acid; Prd = prednisone; Stm = streptomycin; × = for.

* Time to conversion of culture to negative.
¹ Physiological or radiographic parameters measured within days to <3 months of start of therapy.
² Physiological or radiographic parameters measured after 3 months from start of therapy.

uninterpretable [66], because no comparison at all of groups was given.

Therefore, although data suggesting a lack of effect of steroids on acute miliary TB have been presented, enough problems exist with the matching of experimental groups that these data are not interpretable.

**Peritoneal TB**

Singh et al. [67] randomized every other patient with peritoneal TB to receive a prolonged (4-month) course of prednisone (table 7). No specific comment on the comparability of groups was made. The lack of an acute salutary effect of steroids may be explained by the rapid decrease in symptoms seen in both groups. None of 23 corticosteroid-treated patients had chronic fibrotic complications compared with four of 24 controls ($P = NS$, our statistical analysis). Although these investigators emphasized the “desirability of adding steroids to the anti-tuberculous regimen,’’ there seem to be insufficient data from their, or any other, study to recommend this as yet.

**Laryngeal TB**

Despite several reports citing a remarkable diminution in upper airway symptoms when some patients with laryngeal TB received steroid therapy [10, 68, 69], no controlled trial has been performed, and patients’ conditions normally improve rapidly without steroid treatment [69, 70].

**HIV-Associated TB**

No studies have separately examined the use of corticosteroid therapy for HIV-infected patients with TB. Although severe miliary disease with acute respiratory distress syndrome [71, 72], as well as rapid progression to respiratory failure [73], has been observed in HIV-infected patients, only anecdotal

Table 7. Summary of data on adjunctive corticosteroid therapy for peritoneal tuberculosis.

<table>
<thead>
<tr>
<th>Year [reference]</th>
<th>Study design</th>
<th>No. of patients</th>
<th>Antibiotic regimen</th>
<th>Steroid regimen</th>
<th>Endpoints measured</th>
</tr>
</thead>
<tbody>
<tr>
<td>1969 [67]</td>
<td>Randomized by alternate admissions</td>
<td>47 (23 steroid recipients)</td>
<td>INH, Stm; PAS replaced Stm after 3 mo</td>
<td>Prd, 30 mg/d × 3 mo, tapered off over 4th mo</td>
<td>Not mentioned</td>
</tr>
</tbody>
</table>

NOTE. INH = isoniazid; NS = not significant; PAS = para-aminosalicylic acid; Prd = prednisone; Stm = streptomycin; × = for.

* Time to conversion of culture to negative.
¹ Physiological or radiographic parameters measured within days to <3 months of start of therapy.
² Physiological or radiographic parameters measured after 3 months from start of therapy.
data [72] and opinion [74] have been forthcoming, and the adjunctive use of corticosteroid therapy for HIV-related TB must be considered untested.

Discussion

Perusal of four decades of literature on the effects of adjunctive steroid therapy for TB revealed that a tradition of careful clinical investigation has been established by earlier researchers. Adequate data now exist that address the effect of corticosteroids on the course of TB of the lung, pleura, meninges, and pericardium and probably primary disease. Unfortunately, less than adequate data on tuberculous involvement of other organ systems exist.

A recurrent theme has been the persistent efficacy of adequate antimycobacterial therapy in clearing positive cultures even when corticosteroids were used. In eight of 10 studies of pulmonary TB, in which >1,000 patients were included, equal rates of clearance of positive cultures were observed between the matched groups [15–17, 20, 22–24, 26]; the other two studies split on which group cleared faster [19, 25]. These data were similar for the 40 patients in the two studies on primary TB [58, 59]. It would appear that, given the adequacy of antibiotic therapy, there is no slower rate of culture conversion for corticosteroid-treated patients. The Madras study [26] is pertinent for its warning about the necessity for adequate antibiotic therapy, which may be difficult to ensure in areas where multidrug-resistant TB is prevalent.

Most investigations were performed before rifampin was introduced. This agent, combined with isoniazid, has been so effectively tuberculocidal that it could be posited that corticosteroids are not needed in the current era. Indeed, in the Madras trial [26], the trend to faster radiographically evident resolution when corticosteroids were added to rifampin-containing regimens did not reach significance (resolution was significantly faster in the group not given rifampin therapy). However, corticosteroids were beneficial when added to rifampin-containing regimens in three other studies: a double-blind trial studying pleural effusions [50] and both of the studies on tuberculous pericarditis by Strang et al. [43, 44]. No data addressing this question are available from the trials on pulmonary or meningeal TB. Although the addition of corticosteroids to a rapidly tuberculocidical regimen that might prompt a greater local tissue reaction [3] makes sense and is supported by these more recent trials, a final judgment on efficacy must await more trials using the contemporary regimens.

A recurrent objection to the use of corticosteroid therapy for tuberculous meningitis has been the known propensity of these agents to reduce the diffusion of antibacterial agents into the subarachnoid space [75]. However, Kaojarern et al. [76] demonstrated essentially equivalent CSF concentrations when patients treated with and without adjunctive corticosteroids were studied. Isoniazid, rifampin, pyrazinamide, and streptomycin levels were compared in CSF and serum for at least 6 weeks in that study, and although rifampin and streptomycin levels in CSF were not consistently above the MIC for corticosteroid-treated patients, they did not differ from levels in controls. Taken together with the empirical observations from large trials as outlined above, these data suggest that the adjunctive use of corticosteroids does not impair tuberculocidal activity in CSF.

Corticosteroids have been used to suppress hypersensitivity reactions to necessary medicines [77, 78]. Similar data, which are consistent and occasionally striking, have also been generated for the treatment of hypersensitivity reactions to antituberculous agents [79–82]. Three controlled studies [16, 18, 24] specifically examined this effect, and, although it is not clear how vigorously hypersensitivity side effects were actually sought, in general, no obvious protective effect of corticosteroids was observed in these studies. Doses of 20–80 mg of prednisone equivalents were generally used (with 60 mg usually being effective); tapering occurred over 2–8 weeks. Reappearance of hypersensitivity reactions following tapering (usually rashes) was frequent, however, and the continuation of at least a minimal dose of corticosteroids for the entire course of therapy has on occasion been necessary. With the advent of newer, more varied, and non-cross-reacting antituberculous drugs, the necessity of corticosteroid therapy for this indication should be unusual.

An unequivocally lifesaving indication for these agents is adrenal insufficiency secondary to glandular destruction due to TB, a syndrome occurring in from 1% to 58% of patients with TB (depending on the population studied and how vigorously compromised adrenal function was sought) [83–86]. “Stress” doses of corticosteroids should be administered if suspicion of hypoadrenalism arises, at least until the diagnosis is excluded. Attention should be given to the known suppressive effect of rifampin on both exogenous and endogenous metabolism of corticosteroids, which has resulted in the precipitation of adrenal crises following administration by the unwary [87–89].

Recommendations

Sufficient data (at least two adequately performed controlled studies) are available to make recommendations regarding the adjunctive use of corticosteroid therapy for the following disease categories:

1. Pulmonary TB. Adjunctive corticosteroid therapy can be used to relieve the severe systemic and respiratory morbidity of far-advanced pulmonary TB. Radiographically evident abnormalities, other than cavities, usually resolve faster with corticosteroid usage, although the significance to the patient is uncertain. No improvement in final endpoints (chronic respiratory disease or death) can be expected. Given adequate chemotherapy (two or more effective antituberculous agents), adjunctive corticosteroid use does not appear to delay the time to conversion of sputum culture to negative. Dosages of prednisone of 40–60
mg/d (or equivalent) tapered over 4–8 weeks have been shown to be effective.

2. Tuberculous meningitis. The administration of adjunctive corticosteroid therapy to patients with moderate to severe tuberculous meningitis appears to reduce sequelae and improve survival. A faster resolution of abnormal CSF parameters, including elevated pressure, occurs with corticosteroid use and may assist in patient management. Dosages of dexamethasone of 8–12 mg/d (or equivalent) tapered over 6–8 weeks have been used.

3. Tubercular pericarditis. Adjunctive corticosteroids are useful in the management of the acute phase of pericarditis, rapidly reducing the size of pericardial effusions, reducing the need for drainage procedures, and decreasing mortality. A less marked improvement is still evident in the intermediate stages of the disease, although differences in mortality are not so apparent. Corticosteroid administration does not alter the incidence of progression to constrictive disease when used for treatment of either the acute or intermediate stages of pericarditis. Dosages of prednisone of 60 mg/d tapered over 6–12 weeks have been utilized.

4. Tuberculous pleurisy. The pain, dyspnea, and fever associated with this disease appear to resolve much faster with the use of adjunctive corticosteroids. A reduction in subsequent restrictive pleural disease should not be expected. Dosages of prednisone of 20–40 mg/d tapered over 4–8 weeks have been shown to be effective.

Suggestive data (more than one adequate controlled study) are available to make recommendations regarding adjunctive corticosteroid therapy for the following disease category (adequate confirmatory studies are needed in this area):

5. Primary TB. Intrathoracic adenopathy associated with this disease probably involutes faster with the use of adjunctive corticosteroids. Although the dosage of corticosteroids is less well defined, prednisone at 2–5 mg/(kg·d) (or equivalent), dropping over the first week to 1 mg/(kg·d) and then tapering over the next 5 weeks, has been reported to be effective.

Inadequate data (less than two adequate controlled studies) are available to make recommendations regarding adjunctive corticosteroid therapy for the following disease categories (adequate controlled studies are needed):

6. Peritoneal TB. Rapid improvement in the conditions of patients with this disease occurs with antituberculous therapy alone. The single available controlled study showed no convincing advantage to adjunctive corticosteroid therapy for peritoneal TB.

7. Miliary TB. The quality of the available studies prevents a rigorous interpretation of the data, and no recommendation for adjunctive corticosteroid therapy can be made at this time.

8. Laryngeal TB, endobronchial TB, HIV-associated TB, and tuberculous lymphadenitis. No controlled data are available, and no definite recommendations can be made regarding the adjunctive use of corticosteroid therapy for these syndromes.

References