1 Appendix D: Evidence Tables – Treatment of active TB (RQs N & Q)

1.1 RQ N & Q: In people with active TB receiving the standard recommended regimen (isoniazid, rifampicin, pyrazinamide and ethambutol), do corticosteroids as an adjunct to the antituberculosis drug treatment regimen decrease morbidity and mortality compared to the standard recommended regimen alone?

RQ Q has been integrated into this question.

PULMONARY TUBERCULOSIS

1.1.1 Bilaçeroglu et al, 1999

Bibliographic reference	Bilaçeroglu S, Perim K, Büyüksirin M et al (1999) Prednisolone: a beneficial and safe adjunct to antituberculosis treatment? A randomised controlled trial. International Journal of Tuberculosis and Lung Disease 3(1): 47-54
Study type	RCT
Study quality	*Appropriate method of randomisation used?* unclear *Allocation concealment used?* unclear *Blinding used?* only laboratory staff and those reading chest scans were blinded *Groups comparable at baseline?* yes *Groups received the same care apart from the intervention(s) studied?* yes *Groups followed up for an equal and appropriate length of time?* follow-up period was appropriate (1 to 3 years), although it is unclear if it was the same in each group *Groups comparable for treatment completion and availability of outcome data?* yes *Study used precise definitions and reliable measures of outcome?* yes

	Population studied is the same as the population of interest? yes *Intervention used is the same as the intervention of interest?* antituberculosis regimens do not use all of or just the 4 standard recommended drugs *Have substitute outcomes been used instead of the patient-important outcomes of interest?* yes – change in bacillary count is a surrogate for cure/treatment success/treatment failure *Analysis followed the intent-to-treat principle?* yes
Number of patients	Randomised = 178 prednisolone group = 91 antituberculosis chemotherapy alone group = 87 Outcome data available for = 178 prednisolone group = 91 antituberculosis chemotherapy alone group = 87
Patient characteristics	*Inclusion* Advanced pulmonary tuberculosis causing persistent high-grade fever (≥38°C), weight loss (≥2 kg/week) and/or low serum albumin levels (<3 g/dL) HIV-negative *Diagnostic criteria* Confirmed by acid-fast bacilli positivity on smear or culture, and/or granulomatous inflammation with caseous necrosis in the pulmonary biopsy specimen Other febrile causes were excluded by serial blood culture, sputum and urine culture, total body gallium-67

scintigraphy for occult abscesses, screening for occult malignancy, witholding antituberculosis treatment for 3 days to monitor temperature response, and a trial of intravenous broad-spectrum antibiotics for the same 3 days

Exclusion

Accompanying uncontrollable hypertension, recalcitrant diabetes, active or recent peptic ulcer or gastrointestinal bleeding, resistant hypokalemia or florid sepsis

Baseline

	Prednisolone group (n = 91)	**Antituberculosis chemotherapy alone group** (n = 87)
Age (mean±SD), years	36±2.8	34±3.1
Sex, male:female	70:21	64:23
Weight (mean±SD), kg	50.3±1.9	51.1±1.4
Serum albumin level (mean±SD), g/dl	2.57±0.29	2.62±0.17
Fever (mean±SD), °C	38.7±0.4	38.4±0.2
Patients with cavities:patients with miliary lesions	74:17	67:20
Radiographic extent of the disease		
fraction of both lung fields (mean±SD)	7/8±1/8	13/16±1/16
number of patients with bilateral involvement	91	87
Bacillary count on smear (mean±SD)	2±1	2±1

Intervention *Antituberculosis chemotherapy plus prednisolone*

	Prednisolone (40 days) initially administered 20 mg b.i.d IV/IM for 10 days, after which it was given orally and reduced by 10 mg every 10 days Antituberculosis chemotherapy: drug susceptible cases: 3HRZS/3HRE/6HR or 3HRZE/3HRE/6HR drug resistant cases (n = 18): additional drugs (ciprofloxacin, ethionamide and/or amikacin) were given doses not stated
Comparison	*Antituberculosis chemotherapy alone* Antituberculosis chemotherapy: drug susceptible cases: 3HRZS/3HRE/6HR or 3HRZE/3HRE/6HR drug resistant cases (n = 18): additional drugs (ciprofloxacin, ethionamide and/or amikacin) were given doses not stated
Length of follow up	1 to 3 years
Location	Izmir, Turkey
Outcomes measures and effect size	**Mortality** Number of deaths prednisolone group = 0 of 91 antituberculosis chemotherapy alone group = 0 of 87 OR[1] (95% CI) = 0.96 (0.02 to 48.73) i.e. not statistically significant
	Response to treatment – bacillary count Number of to experience a drop in bacillary count 50 days after prednisolone was initiated[3]

	prednisolone group = 91 of 91 antituberculosis chemotherapy alone group = 81 of 87 OR[1] (95% CI) = 14.60 (0.81 to 263.12) i.e. not statistically significant Number of to experience a marked drop in bacillary count 50 days after prednisolone was initiated[3] prednisolone group = 78 of 91 antituberculosis chemotherapy alone group = 54 of 87 **OR[1] (95% CI) = 3.67 (1.77 to 7.61)** **i.e. statistically significant** Time (mean, days) to drop in bacillary count **p = 0.04** **i.e. statistically significant**
	Changes in signs and symptoms – fever Change (mean, °C) in temperature within 72 hours prednisolone group (n = 91) = -1.2 antituberculosis chemotherapy alone group (n = 87) = 0.2 MD[2] = 1.4
	Changes in signs and symptoms – weight change Weight change (mean, kg) during treatment prednisolone group (n = 91) = 7.2 antituberculosis chemotherapy alone group (n = 87) = 4.2

	MD[2] = 3.0 **p = 0.002** **i.e. statistically significant**
	Changes in signs and symptoms – radiographic improvement Radiographic improvement was defined as the combined average percentage of the reductions in the sizes of the initial lesions (infiltrates, cavities and/or pleural effusion): marked (>90%) moderate (50–89%) slight (10–49%) no improvement (<10%) Number of to experience radiographic improvement (marked, moderate or slight) 50 days after prednisolone initiation[3] prednisolone group = 91 of 91 antituberculosis chemotherapy alone group = 83 of 87 OR[1] (95% CI) = 9.86 (0.52 to 185.96) i.e. not statistically significant Number of to experience marked radiographic improvement 50 days after prednisolone initiation[3] prednisolone group = 15 of 91 antituberculosis chemotherapy alone group = 8 of 87 OR[1] (95% CI) = 1.95 (0.78 to 4.86) i.e. not statistically significant
	Relapse

	Number of patients to experience radiographic, bacteriologic or clinical relapse during follow-up prednisolone group = 0 of 91 antituberculosis chemotherapy alone group = 0 of 87 OR[1] (95% CI) = 0.96 (0.02 to 48.73) i.e. not statistically significant
Source of funding	No details provided
Comments	

[1] Odds ratio and 95% confidence interval calculated by reviewer

[2] Mean difference and 95% confidence interval calculated by reviewer

[3] Read off graph by reviewer

Abbreviations: CI, confidence intervals; E, ethambutol; H, isoniazid; OR, odds ratio; R, rifampicin; RCT, randomised controlled trial; S, streptomycin; SD, standard deviation; Z, pyrazinamide

1.1.2 Mayanja-Kizza et al, 2005

Bibliographic reference	Mayanja-Kizza H, Jones-Lopez E, Okwera A et al (2005) Immunoadjuvant prednisolone therapy for HIV-associated tuberculosis: a phase 2 clinical trial in Uganda. Journal of Infectious Diseases 191(6): 856-65
Study type	RCT
Study quality	*Appropriate method of randomisation used?* eligible patients were randomly assigned in blocks of 6 to receive either prednisolone or placebo; the randomisation schedule was developed before the trial by use of computer-generated random numbers with corresponding treatment assignments *Allocation concealment used?* assignments were placed in sealed envelopes and drawn sequentially by a study nurse who was not involved with patient care

	Blinding used? double-blind *Groups comparable at baseline?* fever and night sweats were present in significantly more patients who went on to receive prednisolone than amongst those that went on to receive placebo *Groups received the same care apart from the intervention(s) studied?* yes *Groups followed up for an equal and appropriate length of time?* yes *Groups comparable for treatment completion and availability of outcome data?* yes *Study used precise definitions and reliable measures of outcome?* yes *Population studied is the same as the population of interest?* yes *Intervention used is the same as the intervention of interest?* yes *Have substitute outcomes been used instead of the patient-important outcomes of interest?* yes – event-free survival is a substitute for mortality and adverse events; sputum conversion is a substitute for treatment success; recurrence is a substitute for relapse *Analysis followed the intent-to-treat principle?* yes

Number of patients	Randomised = 187 prednisolone group = 93 placebo group = 94 Treatment completion = 181 prednisolone group = 90 placebo group = 91 Outcome data available after 2 years of follow-up = 136 prednisolone group = 69 placebo group = 67
Patient characteristics	*Inclusion* Initial episodes of acid fast smear–positive pulmonary tuberculosis HIV-infected patients >18 years of age *Exclusion* Previous treatment for tuberculosis Advanced HIV infection (World Health Organization stage IV) Karnofsky performance score <80 Peripheral blood CD4+ T cell count <200 cells/μL Kaposi sarcoma Active herpes zoster Glucose level >160 mg/dL or diabetes mellitus by history

Serum aminotransferase level >65 IU/L

Potassium level >5.5 mmol/L

Positive β-urinary human chorionic gonadotrophin test

Previous use of immunomodulators

Presence or history of hypertension

Psychiatric disease

Peptic ulcer disease

Pancreatitis

Baseline

	Prednisolone group (n = 93)	**Placebo group** (n = 94)
Sex		
males, n (%)	55 (59)	58 (62)
BCG scar present, n (%)	40 (44)	42 (46)
PPD induration		
≥5 mm, n (%)	83 (89)	79 (84)
mean±SD, mm	16±5.4	16±5.4
Karnofsky performance status		
90, n (%)	28 (30)	21 (22)
80, n (%)	60 (65)	68 (72)

		70, n (%)	5 (5)	5 (5)	
		Age (mean±SD), years	31±7.1	31±7.2	
		Body mass index (mean±SD), kg/m^2	19±2.8	19±2.6	
		Haemoglobin level (mean±SD), g/dl	11±1.8	11±1.8	
		White blood cell count (mean±SD), cells/mm^3	8±2.8	7.8±2.8	
		Lymphocyte count (mean±SD), cells/mm^3	1.9±0.8	2.0±0.9	
		Aspartate aminotransferase level (mean±SD), IU/l	26±12	24±12	
		Glucose level (mean±SD), mg/dl	85±24	88±24	
		Potassium level (mean±SD), mmol/dl	4.7±0.4	4.8±0.5	
		Symptoms			
		cough, n (%)	93 (100)	94 (100)	
		chest pain, n (%)	53 (57)	55 (59)	
		hemoptysis, n (%)	5 (5)	11 (12)	
		dyspnea, n (%)	36 (40)	31 (33)	
		fever, n (%)	62 (67)	46 (49)	
		weight loss, n (%)	78 (84)	76 (81)	
		purulent sputum, n (%)	76 (82)	81 (86)	
		night sweats, n (%)	60 (65)	50 (53)	
		Physical examination			
		respiratory			

		consolidation, n (%)	90 (97)	93 (99)	
		wheezing or rhonchi, n (%)	2 (2)	1 (1)	
		pleural effusion, n (%)	0 (0)	1 (1)	
		lymph node enlargement, n (%)	6 (6)	4 (4)	
		sputum smear			
		scanty, n (%)	7 (8)	7 (7)	
		grade 1, n (%)	22 (24)	17 (18)	
		grade 2, n (%)	13 (14)	26 (28)	
		grade 3, n (%)	49 (54)	44 (47)	
		cavitatory	80 (86)	74 (79)	
		chest radiograph finding			
		normal, n (%)	2 (1)	0 (0)	
		minimal, n (%)	3 (3)	4 (4)	
		moderately advanced, n (%)	23 (25)	25 (27)	
		far advanced, n (%)	66 (71)	65 (69)	
Intervention	*Antituberculosis chemotherapy plus prednisolone* Prednisolone (8 weeks) given at a dose of 2.75 mg/kg daily for 4 weeks and tapered over the course of the next 4 weeks to complete an 8-week course Antituberculosis chemotherapy: HRZE – duration and dosing unclear				

	Medications were self-administered
Comparison	*Antituberculosis chemotherapy plus placebo* Placebo (8 weeks) given at a dose of 2.75 mg/kg daily for 4 weeks and tapered over the course of the next 4 weeks to complete an 8-week course Antituberculosis chemotherapy: HRZE – duration and dosing unclear Medications were self-administered
Length of follow up	36 months
Location	Uganda
Outcomes measures and effect size	**Mortality** Number of deaths prednisolone group = 17 of 93 placebo group = 14 of 94 OR[1] (95% CI) = 1.28 (0.59 to 2.77) i.e. not statistically significant
	Event-free survival Number of patients to survive to 36 months without significant adverse event prednisolone group = 36 of 93 placebo group = 40 of 94 OR[1] (95% CI) = 0.85 (0.48 to 1.53) i.e. not statistically significant

	Treatment failure Defined as the failure to clear acid-fast bacilli from the sputum after 5 consecutive months of antituberculous therapy to which the organism was susceptible Number of patients to experience treatment failure prednisolone group = 1 of 93 placebo group = 1 of 94 OR[1] (95% CI) = 1.01 (0.06 to 16.41) i.e. not statistically significant
	Response to treatment – sputum conversion Number of patients to have a sputum culture negative for *M. tuberculosis* after 1 month of treatment prednisolone group = 58 of 93 placebo group = 35 of 94 **OR[1] (95% CI) = 2.79 (1.54 to 5.05)** **i.e. statistically significant** Number of patients to have a sputum culture negative for *M. tuberculosis* after 2 months of treatment prednisolone group = 80 of 93 placebo group = 80 of 94 OR[1] (95% CI) = 1.08 (0.48 to 2.44) i.e. not statistically significant
	Recurrence Defined as the recurrence of active TB after the establishment of cure

	Number of patients to experience recurrence within 2 years of initiating treatment prednisolone group = 8 of 93 placebo group = 11 of 94 OR[1] (95% CI) = 0.71 (0.27 to 1.85) i.e. not statistically significant
	Adverse events Number of patients to experience any adverse event prednisolone group = 87 of 93 placebo group = 82 of 94 OR[1] (95% CI) = 2.55 (0.86 to 7.54) i.e. not statistically significant Number of patients to experience a severe or life-threatening adverse event prednisolone group = 22 of 93 placebo group = 18 of 94 OR[1] (95% CI) = 1.31 (0.65 to 2.64) i.e. not statistically significant
Source of funding	No details provided
Comments	

[1] Odds ratio and 95% confidence interval calculated by reviewer

Abbreviations: BCG, Bacille Calmette-Guerin; CI, confidence intervals; H, isoniazid; OR, odds ratio; PPD, purified protein derivative; R, rifampicin; RCT, randomised controlled trial; S, streptomycin; TB, tuberculosis

1.1.3 Park et al, 1997

Bibliographic reference	Park IW, Choi BW & Hue SH (1997) Prospective study of corticosteroid as an adjunct in the treatment of endobronchial tuberculosis in adults. Respirology 2: 275-81
Study type	RCT
Study quality	*Appropriate method of randomisation used?* unclear *Allocation concealment used?* unclear *Blinding used?* unclear *Groups comparable at baseline?* yes *Groups received the same care apart from the intervention(s) studied?* yes, although details provided are limited *Groups followed up for an equal and appropriate length of time?* not for the full treatment period: only 2 months *Groups comparable for treatment completion and availability of outcome data?* yes *Study used precise definitions and reliable measures of outcome?* yes *Population studied is the same as the population of interest?* yes

<table>
<tr><td></td><td>Intervention used is the same as the intervention of interest?
yes, although some patients received streptomycin instead of ethambutol
Have substitute outcomes been used instead of the patient-important outcomes of interest?
no
Analysis followed the intent-to-treat principle?
unclear</td></tr>
<tr><td>Number of patients</td><td>Randomised = 34
prednisolone group= 17
antituberculosis chemotherapy alone group = 17</td></tr>
<tr><td>Patient characteristics</td><td>Inclusion
Endobronchial tuberculosis
Diagnostic criteria
Endobronchial lesions suggestive of endobronchial tuberculosis – such as cheese-like material, stenosis, granular, ulceration, or inflammatory changes – observed bronchoscopy with either caseating necrosis on tissue biopsy or positive stains/culture of acid-fast bacilli on the sputum, bronchial washing or brushing
Exclusion
Systemic disease or infection
History of previous tuberculosis
Patients who have stopped antituberculosis medications or corticosteroids due to severe side effects
Pregnancy
Baseline
<table>
<tr><th></th><th>Prednisolone group</th><th>Antituberculosis</th></tr>
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			(n = 17)	**chemotherapy alone group** (n = 17)	
		Sex, male:female	3:14	4:13	
		Age			
		15–19, n (%)	3 (33.5)	2 (11.8)	
		20–29, n (%)	8 (47.2)	7 (41.0)	
		30–39, n (%)	1 (5.8)	2 (11.8)	
		40–49, n (%)	4 (23.7)	2 (11.8)	
		50–59, n (%)	1 (5.8)	2 (11.8)	
		>60, n (%)	0 (0)	2 (11.8)	
		Age (mean), years	31.0	34.8	
		Sputum-positive, %	70.6	58.8	
		Pulmonary function			
		FEV1 (mean±SD), % predicted	77.3±16.7	87.0±13.9	
		FVC (mean±SD), % predicted	77.1±21.3	84.6±17.7	
		Posteroanterior chest-x-ray			
		total atelectasis, n	2	0	
		segmental atelectasis, n	3	5	
		Bronchoscopic findings			
		actively caseating, n	12	7	
		stenosis without fibrosis, n	9	9	

	stenosis with fibrosis, n	5	2
	non-specific bronchitic, n	5	6
	glandular, n	2	4
	granular, n	2	2
	ulcerative, n	0	0

Intervention	*Antituberculosis chemotherapy plus prednisolone* Prednisolone (4 to 8 weeks) administered at a dosage of 0.5 mg, approximately 1.0 mg/kg of body weight/day, for 4 to 8 weeks, and then tapered gradually Antituberculosis chemotherapy: HRZS, HRZE or HRZSE dosing and duration not specified
Comparison	*Antituberculosis chemotherapy alone* Antituberculosis chemotherapy: HRZS, HRZE or HRZSE dosing and duration not specified
Length of follow up	2 months after treatment initiation
Location	Seoul, Korea
Outcomes measures and effect size	**Change in signs and symptoms – endobronchial lesions** Including actively caseating lesions, stenosis with and without fibrosis, glandular-type lesions and granular-type lesions Number of endobronchial lesions identified using bronchoscopy before treatment to have improved after 2 months of treatment prednisolone group= 24 of 35

	antituberculosis chemotherapy alone group = 22 of 30 OR[1] (95% CI) = 0.79 (0.27 to 2.33) i.e. not statistically significant
	Change in signs and symptoms – pulmonary lesions Including atelectasis, patchy infiltration, fibrostreaky density, hilar mass shadow, nodular lesions and cavitatory lesions Number of lesions identified using chest-x-ray before treatment to have improved after 2 months of treatment prednisolone group= 22 of 29 antituberculosis chemotherapy alone group = 23 of 28 OR[1] (95% CI) = 0.68 (0.19 to 2.48) i.e. not statistically significant
Source of funding	No details provided
Comments	

[1] Odds ratio and 95% confidence interval calculated by reviewer

Abbreviations: CI, confidence intervals; E, ethambutol; H, isoniazid; OR, odds ratio; R, rifampicin; RCT, randomised controlled trial; S, streptomycin; SD, standard deviation; Z, pyrazinamide

1.1.4 Tuberculosis Research Centre (Madras), 1983

Bibliographic reference	Tuberculosis Research Centre (Madras) (1983) Study of chemotherapy regimens of 5 and 7 months' duration and the role of corticosteroids in the treatment of sputum-positive patients with pulmonary tuberculosis in South India. Tuberculosis Research Centre. Tubercle 64: 73-91
Study type	RCT
Study quality	*Appropriate method of randomisation used?* unclear

	Allocation concealment used? unclear *Blinding used?* unclear *Groups comparable at baseline?* yes *Groups received the same care apart from the intervention(s) studied?* yes *Groups followed up for an equal and appropriate length of time?* yes *Groups comparable for treatment completion and availability of outcome data?* unclear *Study used precise definitions and reliable measures of outcome?* yes *Population studied is the same as the population of interest?* yes *Intervention used is the same as the intervention of interest?* yes, although patients received streptomycin instead of ethambutol, and some patients did not receive rifampicin *Have substitute outcomes been used instead of the patient-important outcomes of interest?* yes – sputum conversion is a substitute for cure/treatment failure *Analysis followed the intent-to-treat principle?*

	unclear
Number of patients	Randomised = 530 prednisolone group = 261 antituberculosis chemotherapy alone group = 269 Outcome data available at 24 months = 530 prednisolone group = 261 antituberculosis chemotherapy alone group = 269
Patient characteristics	*Inclusion* Newly diagnosed pulmonary tuberculosis Aged ≥12 years *Diagnostic criteria* At least 2 positive sputum cultures *Baseline* Unclear
Intervention	*Antituberculosis chemotherapy plus prednisolone* Prednisolone (8 weeks) 20 mg 3 times/day (except Sundays) for the first week, 3 doses of 10 mg, 5 mg, and 5 mg daily for the next 5 weeks, 5 mg twice-daily in the 7^{th} week and 5 mg daily in the eighth week Antituberculosis chemotherapy: $2SHRZ_7/3SHZ_2$, $2SHRZ_7/5SHZ_2$ or $2SHZ_7/5SHZ$ isoniazid at 400 mg/day during initial phase, followed by 15 mg/kg of body weight/day thereafter, rifampicin at 12 mg/kg of body weight/day, pyrazinamide at 40 mg/kg of body weight/day, and streptomycin at 750 mg/kg of body weight/day

	Treated as outpatients, though were given their drugs under close supervision by a clinic nurse
Comparison	*Antituberculosis chemotherapy alone* Antituberculosis chemotherapy: $2SHRZ_7/3SHZ_2$, $2SHRZ_7/5SHZ_2$ or $2SHZ_7/5SHZ$ isoniazid at 400 mg/day during initial phase, followed by 15 mg/kg of body weight/day thereafter, rifampicin at 12 mg/kg of body weight/day, pyrazinamide at 40 mg/kg of body weight/day, and streptomycin at 750 mg/kg of body weight/day Treated as outpatients, though were given their drugs under close supervision by a clinic nurse
Location	Madras, India
Length of follow up	24 months
Outcomes measures and effect size	**Response to treatment – sputum conversion** Number of patients with all cultures negative after 1 month of treatment prednisolone group = 81 of 261 antituberculosis chemotherapy alone = 80 of 269 OR[1] (95% CI) = 1.06 (0.73 to 1.54) i.e. not statistically significant Number of patients with all cultures negative after 2 months of treatment prednisolone group = 167 of 261 antituberculosis chemotherapy alone = 167 of 269 OR[1] (95% CI) = 1.09 (0.76 to 1.54) i.e. not statistically significant Number of patients with all cultures negative after 3 months of treatment prednisolone group = 187 of 261

	antituberculosis chemotherapy alone = 183 of 269 OR[1] (95% CI) = 1.19 (0.82 to 1.72) i.e. not statistically significant
	Changes in signs and symptoms – radiographic improvement Number of patients to achieve moderate or greater radiographic improvement after 2 months of treatment prednisolone group = 130 of 261 antituberculosis chemotherapy alone = 107 of 269 **OR[1] (95% CI) = 1.50 (1.06 to 2.12)** **i.e. statistically significant** Number of patients in whom cavitation was present on admission but disappeared by the end of treatment prednisolone group = 103 of 245 antituberculosis chemotherapy alone = 88 of 250 OR[1] (95% CI) = 1.34 (0.93 to 1.92) i.e. not statistically significant Number of patients in whom the cavitation that was present on admission had lessened by the end of treatment prednisolone group = 97 of 245 antituberculosis chemotherapy alone = 111 of 250 OR[1] (95% CI) = 0.82 (0.57 to 1.17) i.e. not statistically significant
	Relapse Defined as 2 or more cultures positive for *M. tuberculosis* out of 6 examined in any 3 consecutive monthly

	examinations up to 24 months after treatment initiation, or in any 4 consecutive monthly examinations beyond 24 months Number to experience bacteriological relapse requiring treatment prednisolone group = 5 of 261 antituberculosis chemotherapy alone = 6 of 269 OR[1] (95% CI) = 0.86 (0.26 to 2.84) i.e. not statistically significant
Source of funding	No details provided
Comments	

[1] Odds ratio and 95% confidence interval calculated by reviewer

Abbreviations: CI, confidence intervals; H, isoniazid; OR, odds ratio; R, rifampicin; RCT, randomised controlled trial; S, streptomycin; TB, tuberculosis

PLEURAL TUBERCULOSIS

1.1.5 Elliott et al, 2004

Bibliographic reference	Elliott AM, Luzze H, Quigley MA et al (2004) A randomised, double-blind, placebo-controlled trial of the use of prednisolone as an adjunct to treatment in HIV-1-associated pleural tuberculosis. Journal of Infectious Diseases 190: 869-78
Study type	RCT
Study quality	*Appropriate method of randomisation used?* yes – computer-generated randomisation sequence *Allocation concealment used?* yes – sequence was generated by a statistician who was not involved in the care of the patients; prednisolone and matching placebo tablets were packaged in identical plastic bags labelled with randomisation code numbers by 2 people who were not involved in the study *Blinding used?* yes – sequence was generated by a statistician who was not involved in the care of the patients; prednisolone and matching placebo tablets were packaged in identical plastic bags labelled with randomisation code numbers by 2 people who were not involved in the study; medical staff gave participants the next number in the sequence in the order in which they were enrolled; all participants and medical, laboratory, and statistical staff remained blinded to the treatment allocation until all data collection had been completed *Groups comparable at baseline?* yes *Groups received the same care apart from the intervention(s) studied?* yes *Groups followed up for an equal and appropriate length of time?*

	yes *Groups comparable for treatment completion and availability of outcome data?* yes *Study used precise definitions and reliable measures of outcome?* yes *Population studied is the same as the population of interest?* yes *Intervention used is the same as the intervention of interest?* yes *Have substitute outcomes been used instead of the patient-important outcomes of interest?* yes – recurrence is a substitute for relapse *Analysis followed the intent-to-treat principle?* yes
Number of patients	Randomised = 297 prednisolone group = 99 antituberculosis chemotherapy alone group = 98 Outcome data available at 24 weeks for anorexia, weight and cough = 151 prednisolone group = 80 antituberculosis chemotherapy alone group = 71 Outcome data available at 24 weeks for residual effusion = 148 prednisolone group = 76

<table>
<tr><td></td><td>antituberculosis chemotherapy alone group = 72</td></tr>
<tr><td>Patient characteristics</td><td>
Inclusion

Presented with clinical features suggesting pleural tuberculosis, with a pleural effusion occupying at least one-third of 1 hemithorax (as determined by a radiograph)

≥18 years old

HIV-1-associated

Residents of Kampala

Diagnostic criteria

Pleural tuberculosis was considered to be confirmed if a patient had a positive culture for Mycobacterium tuberculosisfrom pleural biopsy tissue, pleural fluid, or sputum or if histopathologic analysis of pleural tissue was consistent with tuberculous pleurisy

Exclusion

Previous treatment or prophylaxis for tuberculosis

Recent treatment with glucocorticoids

Pregnant or breast-feeding

Baseline
<table>
<tr><th></th><th>Prednisolone group
(n = 98)</th><th>Placebo group
(n = 99)</th></tr>
<tr><td>Sex
males, n
females, n</td><td>
54
45</td><td>
60
38</td></tr>
<tr><td>Age (mean±SD), years</td><td>34±9</td><td>34±8</td></tr>
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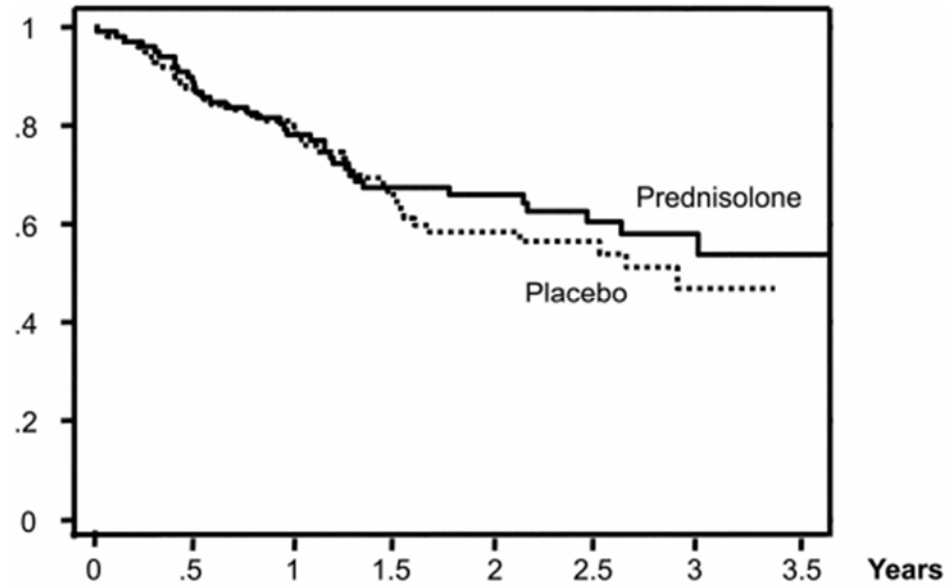
		Weight (mean±SD), kg	54±9	53±8	
		Blood pressure			
		systolic (mean±SD), mm Hg	102±13	101±10	
		diastolic (mean±SD), mm Hg	73±11	72±11	
		Symptoms			
		fever, n	66	60	
		cough, n	91	84	
		dyspnea, n	83	86	
		chest pain, n	84	82	
		anorexia, n	72	77	
		weight loss, n	86	83	
		Signs			
		fever ≥37.5°C, n	55	53	
		Karnofsky score ≥80%, n	59	49	
		oral thrus, n	9	5	
		herpes zoster scars, n	13	12	
		lymphadenopathy, n	12	11	
		Laboratory findings			
		CD4+ count (median (interquartile range)), cells/μl	118 (57–211)	93 (58–219)	
		confirmed tuberculosis, n	89	91	

		isoniazid resistance, n	5	5
		pyrazinamide resistance, n	1	0
		Radiography findings		
		1 zone affected, n	14	18
		2 zones affected, n	49	46
		≥3 zones affected, n	33	33
Intervention	*Antituberculosis chemotherapy plus prednisolone* Prednisolone (8 weeks) supplied as 5-mg tablets and was given concomitantly with tuberculous therapy at a dosage of 50 mg daily for 2 weeks, followed by 40 mg daily for 2 weeks, followed by 25 mg daily for 2 weeks, followed by 15 mg daily for 2 weeks; prednisolone treatment was then stopped Antituberculosis chemotherapy: 2HRZE/4HR doses were adjusted according to each patient's weight, using the American Thoracic Society's standard criteria Participants either were admitted to the tuberculosis ward or (in exceptional circumstances) attended the ward daily, for directly observed treatment for 1 week			
Comparison	*Antituberculosis chemotherapy plus placebo* Placebo (8 weeks) supplied as 5-mg tablets and was given concomitantly with tuberculous therapy at a dosage of 50 mg daily for 2 weeks, followed by 40 mg daily for 2 weeks, followed by 25 mg daily for 2 weeks, followed by 15 mg daily for 2 weeks; placebo treatment was then stopped Antituberculosis chemotherapy: 2HRZE/4HR doses were adjusted according to each patient's weight, using the American Thoracic Society's standard criteria			

	Participants either were admitted to the tuberculosis ward or (in exceptional circumstances) attended the ward daily, for directly observed treatment for 1 week
Length of follow up	42 months
Location	Kampala, Uganda
Outcomes measures and effect size	**Mortality** Mortality rate (deaths/100 person years) prednisolone group (n = 99) = 21 antituberculosis chemotherapy alone group (n = 98) = 25 RR (95% CI) = 0.84 (0.53 to 1.32) i.e. not statistically significant Kaplan-Meier survival curve



Changes in signs and symptoms – anorexia

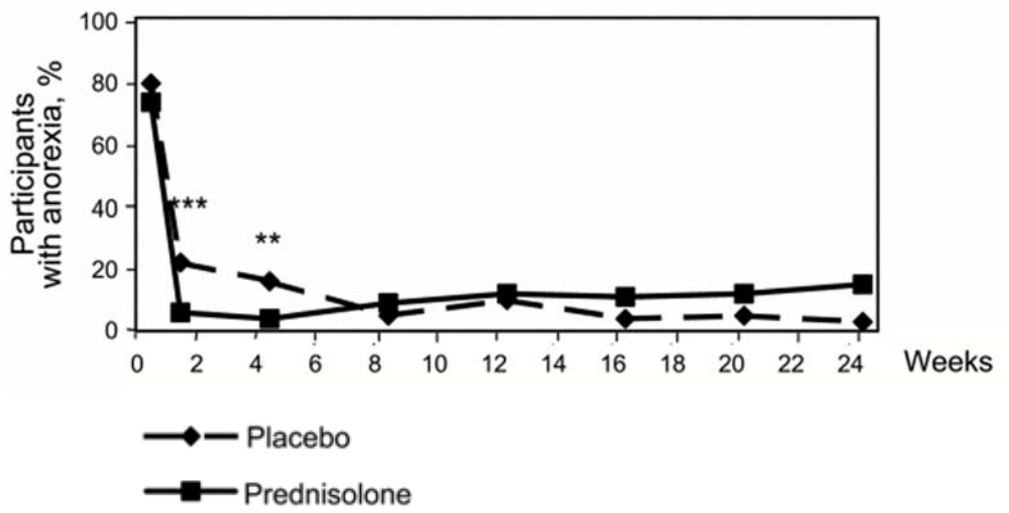
Number of patients to be anorexic after 24 weeks of treatment[2]

prednisolone group = 12 of 99

antituberculosis chemotherapy alone group = 3 of 98

OR[1] (95% CI) = 4.37 (1.19 to 16.00)

i.e. statistically significant



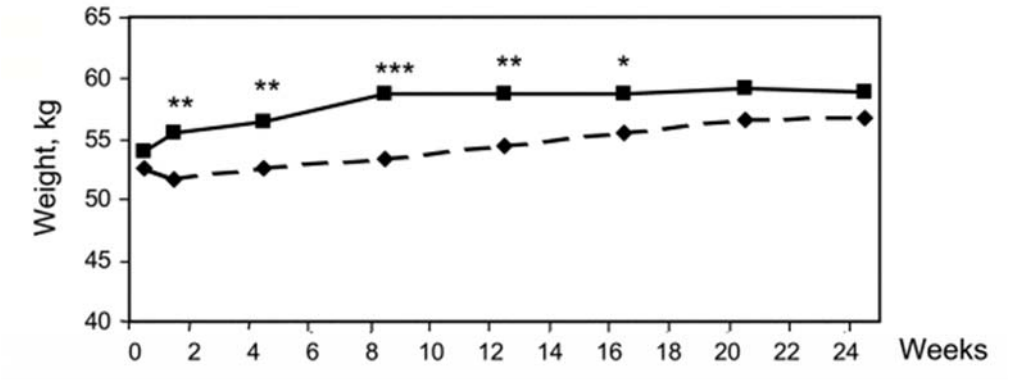
Changes in signs and symptoms – weight

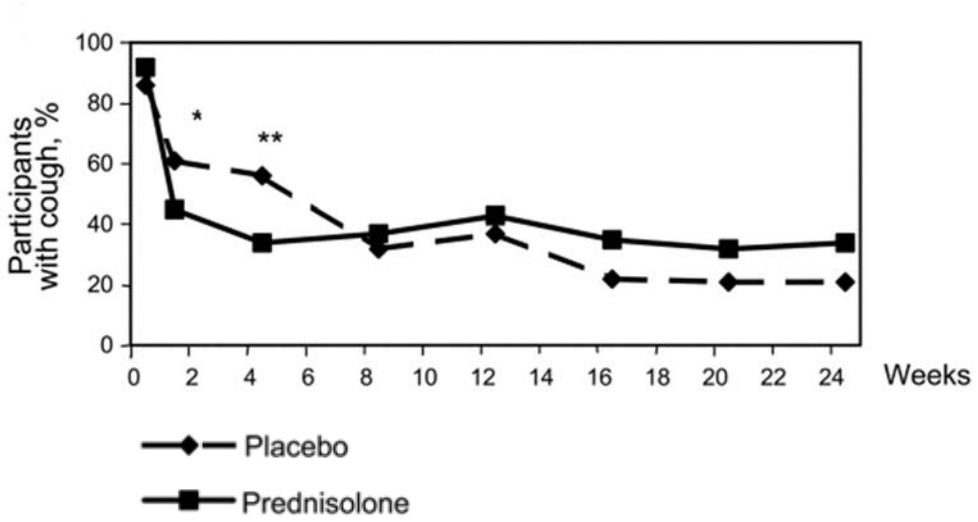
Weight (mean, kg) after 24 weeks of treatment[2]

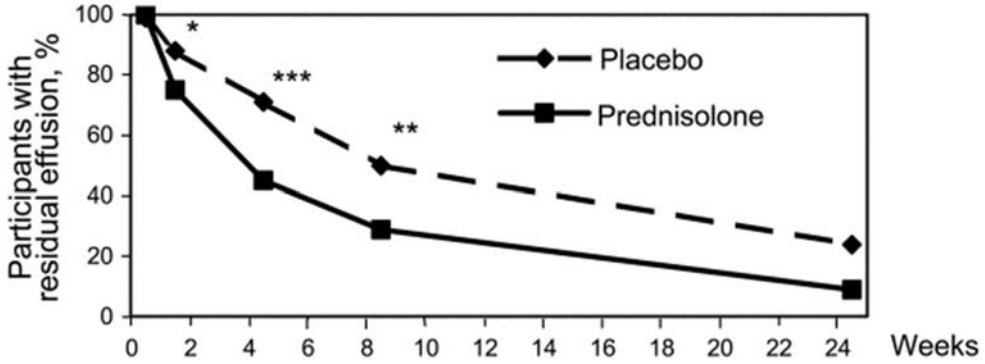
prednisolone group = 59

antituberculosis chemotherapy alone group = 56

MD[3] = 3 kg



	Placebo Prednisolone
	Changes in signs and symptoms – cough Number of patients with a cough after 24 weeks of treatment[2] prednisolone group = 26 of 99 antituberculosis chemotherapy alone group = 14 of 98 **OR[1] (95% CI) = 2.14 (1.04 to 4.40)** **i.e. statistically significant** 
	Changes in signs and symptoms – pleural effusion Number of patients with pleural effusion after 24 weeks of treatment[2] prednisolone group = 7 of 99

	antituberculosis chemotherapy alone group = 17 of 98 **OR[1] (95% CI) = 0.36 (0.14 to 0.92)** **i.e. statistically significant** 
	Recurrence Recurrence rate (cases/100 person years) prednisolone group = 4.5 antituberculosis chemotherapy alone group = 1.8 RR (95% CI) = 2.3 (0.6 to 9.0) i.e. not statistically significant
	Adverse events requiring treatment discontinuation Number of patients to experience an adverse event that required discontinuation of placebo/prednisolone prednisolone group = 9 of 99 antituberculosis chemotherapy alone group = 2 of 98 **OR[1] (95% CI) = 4.80 (1.01 to 22.82)**

	i.e. statistically significant
	Adverse events – incidence of HIV-related disease Number of patients to experience Kaposi sarcoma prednisolone group = 6 of 99 antituberculosis chemotherapy alone group = 0 of 98 OR[1] (95% CI) = 13.70 (0.76 to 246.52) i.e. not statistically significant Number of patients to experience cryptococcal meningitis prednisolone group = 3 of 99 antituberculosis chemotherapy alone group = 5 of 98 OR[1] (95% CI) = 0.58 (0.14 to 2.50) i.e. not statistically significant Number of patients to experience oesophageal candidiasis prednisolone group = 35 of 99 antituberculosis chemotherapy alone group = 23 of 98 OR[1] (95% CI) = 1.78 (0.96 to 3.32) i.e. not statistically significant Number of patients to experience herpes zoster prednisolone group = 22 of 99 antituberculosis chemotherapy alone group = 19 of 98 OR[1] (95% CI) = 1.19 (0.60 to 2.37)

	i.e. not statistically significant Number of patients to experience oral or genital herpes simplex prednisolone group = 22 of 99 antituberculosis chemotherapy alone group = 20 of 98 OR[1] (95% CI) = 1.11 (0.56 to 2.21) i.e. not statistically significant Number of patients to experience oral thrush prednisolone group = 31 of 99 antituberculosis chemotherapy alone group = 31 of 98 OR[1] (95% CI) = 1.43 (0.79 to 2.56) i.e. not statistically significant Number of patients to experience gastroenteritis prednisolone group = 34 of 99 antituberculosis chemotherapy alone group = 28 of 98 OR[1] (95% CI) = 1.31 (0.72 to 2.39) i.e. not statistically significant
Source of funding	Details not provided
Comments	

[1] Odds ratio and 95% confidence interval calculated by reviewer

[2] Read off graph by reviewer

[3] Mean difference calculated by reviewer

Abbreviations: CI, confidence intervals; E, ethambutol; H, isoniazid; OR, odds ratio; R, rifampicin; RCT, randomised controlled trial; RR, rate ratio; Z, pyrazinamide

1.1.6 Galarza et al, 1995

Bibliographic reference	Galarza I, Cañete C, Granados A et al (1995) Randomised trial of corticosteroids in the treatment of tuberculous pleurisy. Thorax 50: 1305-7
Study type	RCT
Study quality	*Appropriate method of randomisation used?* unclear *Allocation concealment used?* unclear *Blinding used?* double-blind *Groups comparable at baseline?* yes *Groups received the same care apart from the intervention(s) studied?* yes, although the details provided were limited *Groups followed up for an equal and appropriate length of time?* yes *Groups comparable for treatment completion and availability of outcome data?* yes *Study used precise definitions and reliable measures of outcome?*

<table>
<tr><td></td><td>yes
Population studied is the same as the population of interest?
yes
Intervention used is the same as the intervention of interest?
yes, although patients received only 2 drugs, lacking ethambutol and pyrazinamide
Have substitute outcomes been used instead of the patient-important outcomes of interest?
no
Analysis followed the intent-to-treat principle?
yes</td></tr>
<tr><td>Number of patients</td><td>Randomised = 117
prednisolone group = 57
placebo group = 60</td></tr>
<tr><td>Patient characteristics</td><td>Inclusion
Pleural effusion of tuberculous aetiology
Exclusion
HIV infection
Baseline
Definite microbiological or pathological diagnosis was obtained in 63% of patients
<table>
<tr><th></th><th>Prednisolone group
(n = 57)</th><th>Placebo group
(n = 60)</th></tr>
<tr><td>Age (mean (range)), years</td><td>26 (11–53)</td><td>28 (14–53)</td></tr>
</table></td></tr>
</table>

<table>
<tr><td></td><td>
<table>
<tr><td>Sex, male:female</td><td>33:27</td><td>30:31</td></tr>
<tr><td>Side
right, n (%)
left, n (%)</td><td>
34
23</td><td>
36
24</td></tr>
<tr><td>Fever (mean (range)), days</td><td>3.32 (0–50)</td><td>4.15 (0–60)</td></tr>
<tr><td>Thickening (mean (range)), mm</td><td>1.77 (0–40)</td><td>2.23 (0–15)</td></tr>
<tr><td>FVC (mean (range)), % predicted</td><td>95 (65–130)</td><td>95 (63–140)</td></tr>
<tr><td>Follow-up (mean (range)), months</td><td>46 (12–94)</td><td>46 (12–96)</td></tr>
</table>
</td></tr>
<tr><td>Intervention</td><td>Antituberculosis chemotherapy plus prednisolone

Prednisolone (30 days)

administered in a single oral dose of 1 mg/kg of body weight/day during the first 15 days, and then gradually tapered off as follows: to 0 5 mg/kg of body weight/day from day 16-20 of treatment, then to 0-25 mg/ kg of body weight/day from day 21-26, and finally to 0 10 mg/kg of body weight/day for the remaining days of the month

Antituberculosis chemotherapy: 6HR

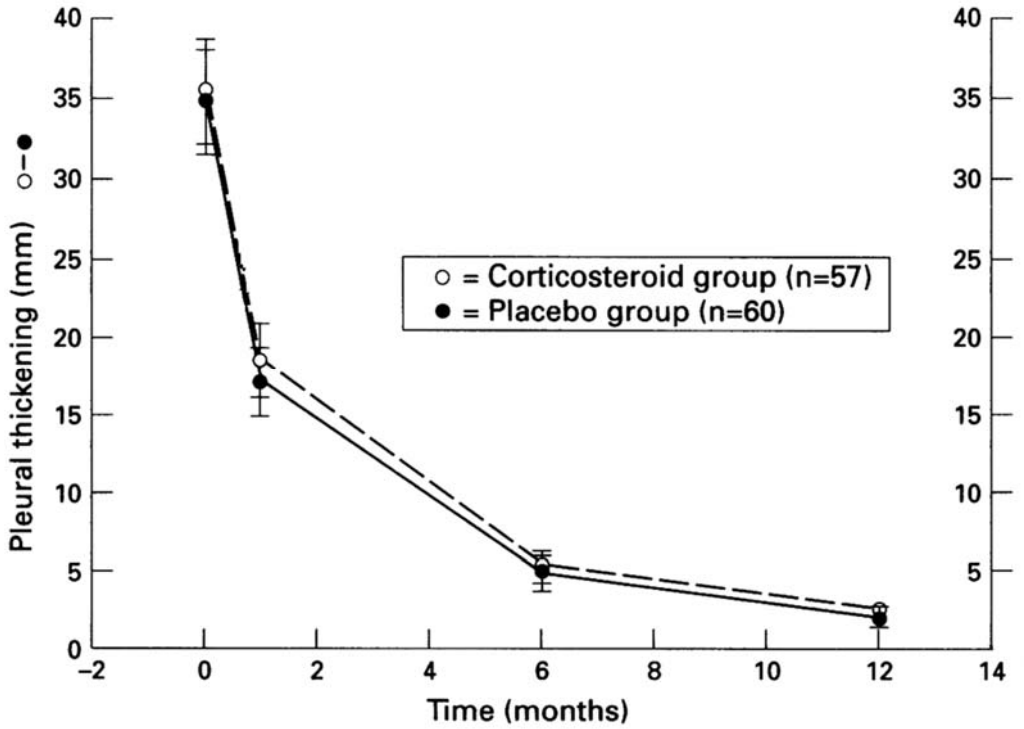
isoniazid, 5 mg/kg/day or a total daily dose of 300 mg, and rifampicin, 10 mg/kg of body weight/day or a total daily dose of 600 mg/day, once a day for six months as a combination tablet</td></tr>
<tr><td>Comparison</td><td>Antituberculosis chemotherapy plus placebo

Placebo (30 days)

administered in a single oral dose of 1 mg/kg of body weight/day during the first 15 days, and then gradually tapered off as follows: to 0 5 mg/kg of body weight/day from day 16-20 of treatment, then to 0-25 mg/ kg of body weight/day from day 21-26, and finally to 0 10 mg/kg of body weight/day for the remaining days of the month

Antituberculosis chemotherapy: 6HR</td></tr>
</table>

	isoniazid, 5 mg/kg/day or a total daily dose of 300 mg, and rifampicin, 10 mg/kg of body weight/day or a total daily dose of 600 mg/day, once a day for six months as a combination tablet
Length of follow up	46 months
Location	Barcelona, Spain
Outcomes measures and effect size	**Changes in signs and symptoms – pleural thickening** Number of patients to show pleural thickening at 12 months, as assessed using a chest x-ray prednisolone group = 1 of 57 placebo group = 5 of 60 OR[2] (95% CI) = 0.20 (0.02 to 1.74) i.e. not statistically significant Pleural thickening (mean (range), days) at 46 months, as assessed using a chest x-ray prednisolone group (n = 57) = 1.77 (0–40) placebo group (n = 60) = 2.23 (0–15) MD[3] = -0.46



Changes in signs and symptoms – pleural hemithorax reabsorption

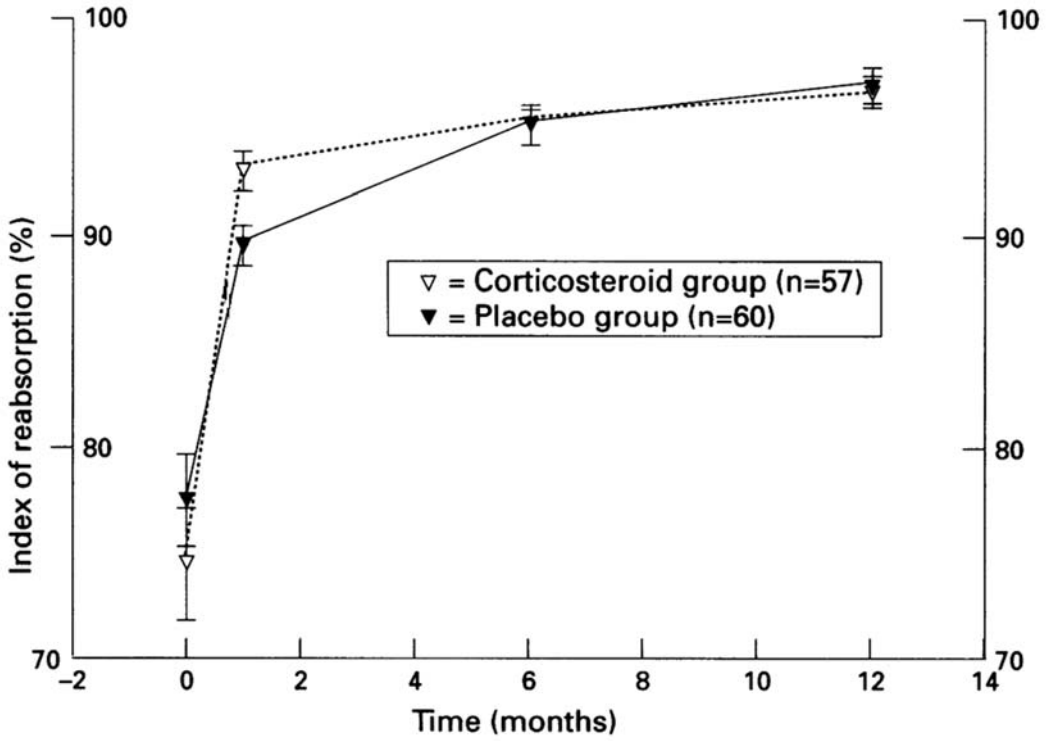
Index of reabsorption (mean±SE (range), %) at 12 months[1]

prednisolone group (n = 57) = 93±8 (70–119)

placebo group (n = 60) = 89±8 (76–113)

MD[3] (95% CI) = 4 (-18 to 26)

i.e. not statistically significant

	
	Changes in signs and symptoms – fever Duration of fever (mean (range), days) at 46 months prednisolone group (n = 57) = 3.32 (0–50) placebo group (n = 60) = 4.15 (0–60) MD[3] = -0.83
Source of funding	Fondo de Investigaciones de la Seguridad Social
Comments	

[1] Standard error read of the graph by reviewer

[2] Odds ratio and 95% confidence intervals, where possible, calculated by reviewer

[3] Mean difference and 95% confidence intervals, where possible, calculated by reviewer

Abbreviations: CI, confidence intervals; H, isoniazid; MD, mean difference; OR, odds ratio; R, rifampicin; RCT, randomised controlled trial; S, streptomycin; SE, standard error

1.1.7 Lee et al, 1988

Bibliographic reference	Lee C-H, Wang W-J, Lan R-S et al (1988) Corticosteroids in the treatment of tuberculosis pleurisy. A double-blind, placebo-controlled, randomised study. Chest 94(6): 1256-9
Study type	RCT
Study quality	*Appropriate method of randomisation used?* unclear *Allocation concealment used?* unclear *Blinding used?* unclear *Groups comparable at baseline?* yes *Groups received the same care apart from the intervention(s) studied?* yes, although details provided are limited *Groups followed up for an equal and appropriate length of time?* yes *Groups comparable for treatment completion and availability of outcome data?*

	yes *Study used precise definitions and reliable measures of outcome?* yes *Population studied is the same as the population of interest?* yes *Intervention used is the same as the intervention of interest?* yes, although patients did not receive pyrazinamide *Have substitute outcomes been used instead of the patient-important outcomes of interest?* no *Analysis followed the intent-to-treat principle?* no
Number of patients	Randomised = 45 Outcome data available for = 40 prednisolone group = 21 placebo group = 19
Patient characteristics	*Inclusion* Onset of pleural effusion without previous treatment; other aetiologies of pleural effusion, such as congestive heart failure, pneumonia and malignancy, were excluded through diagnostic testing Aged <45 years *Diagnostic criteria* Diagnosis of tuberculous pleurisy was confirmed on the basis of pleural biopsy

<table>
<tr><td></td><td>
Exclusion
Other diseases or pulmonary diseases
Conditions that contraindicated the use of corticosteroids, such as diabetes, peptic ulcer or hypertension
Baseline
<table>
<tr><th></th><th>Prednisolone group
(n = 21)</th><th>Placebo group
(n = 19)</th></tr>
<tr><td>Sex</td><td></td><td></td></tr>
<tr><td>male, n</td><td>12</td><td>12</td></tr>
<tr><td>female, n</td><td>9</td><td>7</td></tr>
<tr><td>Age (mean (range)), years</td><td>28.4 (18–44)</td><td>28.9 (18–45)</td></tr>
<tr><td>Time from onset of symptoms to diagnosis (mean), days</td><td>20.6</td><td>15.4</td></tr>
<tr><td>Initial amount of pleural effusions[1]</td><td></td><td></td></tr>
<tr><td>small, n</td><td>9</td><td>5</td></tr>
<tr><td>moderate, n</td><td>9</td><td>9</td></tr>
<tr><td>large, n</td><td>3</td><td>5</td></tr>
</table>
</td></tr>
<tr><td>Intervention</td><td>
Antituberculosis chemotherapy plus prednisolone
Prednisolone
administered in an oral dose of 0.75 mg/kg of body weight/day initially
the dosage was tapered once the chest radiograph showed improvement
the dosage was diminished by two-thirds if any of the following conditions existed: 1) the effusion was right-sided and
</td></tr>
</table>

	the fluid level was only one intercostal space higher than that of the left hemidiaphragm, 2) the effusion was left-sided and the fluid level was at the same height as the right hemidiaphragm, or 3) complete disappearance of pleural effusion; the dosage of prednisolone was then diminished by 5 mg/week until discontinued Antituberculosis chemotherapy: 3HRE/6-9HR isoniazid at 300 mg/day, rifampicin at 450 mg/day, ethambutol at 20 mg/kg of body weight/day for the initial 3 months, followed by isoniazid and rifampicin at the same doses for the subsequent 6 to 9 months
Comparison	*Antituberculosis chemotherapy plus placebo* Placebo administered in an oral dose of 0.75 mg/kg of body weight/day initially the dosage was tapered once the chest radiograph showed improvement the dosage was diminished by two-thirds if any of the following conditions existed: 1) the effusion was right-sided and the fluid level was only one intercostal space higher than that of the left hemidiaphragm, 2) the effusion was left-sided and the fluid level was at the same height as the right hemidiaphragm, or 3) complete disappearance of pleural effusion; the dosage of prednisolone was then diminished by 5 mg/week until discontinued Antituberculosis chemotherapy: 3HRE/6-9HR isoniazid at 300 mg/day, rifampicin at 450 mg/day, ethambutol at 20 mg/kg of body weight/day for the initial 3 months, followed by isoniazid and rifampicin at the same doses for the subsequent 6 to 9 months
Length of follow up	Exact period unclear, though at least 1 year
Location	Taipei, Taiwan
Outcomes measures and effect size	**Change in signs and symptoms – disappearance of clinical signs and symptoms** Time (mean±SD[2] (range), days) to disappearance of clinical signs and symptoms (including fever, chest pain and dyspnea) prednisolone group (n = 21) = 2.4±1.6 (1–7) placebo group (n = 19) = 9.2±16.5 (1–75) $p<0.05$

	MD[3] (95% CI) = -6.8 (-14.3 to 0.7) i.e. not statistically significant
	Change in signs and symptoms – pleural effusion Time (mean[4] (range), days) to clearance of pleural effusion (as defined by roentgenologic evidence of clearing of the lung field, with visualisation of the diaphragm and costophrenic angle) prednisolone group (n = 21) = 54.5 (6–365) placebo group (n = 19) = 123.2 (7–395) **p<0.01** **MD[3] = -68.7**
	Change in signs and symptoms – pleural adhesions Number of patients to experience pleural adhesions prednisolone group = 1 of 21 placebo group = 3 of 19 p = 0.27 OR[5] (95% CI) = 0.27 (0.03 to 2.82) i.e. not statistically significant
Source of funding	No details provided
Comments	

[1] Small = less than one-third of one hemithorax; moderate = between one-third and two-thirds of one hemithorax; large = morTime (e than two-thirds of one hemithorax

[2] Standard deviation calculated from the individual patient data read off the graph by reviewer

[3] Mean difference and 95% confidence intervals, where possible, calculated by reviewer

[4] Standard deviation could not be calculated by reviewer as individual patient data could not be read off the graph

[5] Odds ratio and 95% confidence intervals calculated by reviewer

Abbreviations: CI, confidence intervals; E, ethambutol; H, isoniazid; MD, mean difference; OR, odds ratio; R, rifampicin; RCT, randomised controlled trial; SD, standard deviation

1.1.8 Wyser et al, 1996

Bibliographic reference	Wyser C, Walzl G, Smedema JP et al (1996) Corticosteroids in the treatment of tuberculous pleurisy. A double-blind, placebo-controlled, randomised study. Chest 110(2): 333-8
Study type	RCT
Study quality	*Appropriate method of randomisation used?* unclear *Allocation concealment used?* unclear *Blinding used?* double-blind *Groups comparable at baseline?* although not statistically significant (p = 0.06), more patients receiving placebo (44.4%) had pleuritis *and* pulmonary tuberculosis than amongst those receiving prednisolone (21.2) *Groups received the same care apart from the intervention(s) studied?* yes, although details provided are limited *Groups followed up for an equal and appropriate length of time?* follow-up not for the full treatment period *Groups comparable for treatment completion and availability of outcome data?*

	yes *Study used precise definitions and reliable measures of outcome?* yes *Population studied is the same as the population of interest?* yes *Intervention used is the same as the intervention of interest?* yes, although patients did not receive ethambutol *Have substitute outcomes been used instead of the patient-important outcomes of interest?* yes – 'morbidity' is a patient-reported, surrogate outcome made of a composite of well-being, appetite, night sweats, pleuritic chest pain, tiredness, dyspnea and cough *Analysis followed the intent-to-treat principle?* no
Number of patients	Randomised = 74 Outcome data available for = 70 prednisolone group = 34 placebo group = 36
Patient characteristics	*Inclusion* Exudative pleural effusions Biopsy specimen-proven tuberculous pleurisy *Diagnostic criteria* Diagnosis confirmed by the presence of caseating granulomas with or without acid-fast bacilli on histologic study and/or a positive *M. tuberculosis* culture

Exclusion

Other causes of pleural exudates, such as pneumonia or malignancy

Contraindications to corticosteroid use, such as diabetes mellitus, uncontrolled hypertension, peptic ulcer disease and empyema

HIV-seropositive

Neoplastic disease

Baseline

	Prednisolone group (n = 34)	**Placebo group** (n = 36)
Sex		
male, %	61.8	61.2
Age (mean±SD), years	32.9±13.0	32.8±12.5
Duration of illness prior to hospital admission (mean±SD), weeks	2.9±2.7	3.7±2.2
Pleuritis only, %	78.8	55.6
Pleuritis and pulmonary tuberculosis	21.2	44.4
Initial amount of pleural effusions on chest x-ray		
small, %	2.9	0
moderate, %	14.7	13.9
large, %	82.4	86.1
Positive M. tuberculosis culture		
pleural fluid, %	8.8	13.9

	pleural biopsy specimen, %	78.8	77.8
	bronchial lavage, %	14.7	8.6
	Histology		
	caseating granuloma, %	93.7	91.7
	non-caseating granuloma, %	6.1	8.3
	Ziehl-Neelsen positive, %	51.5	47.2
	Appearance on thoracoscopy[1]		
	type 1	9.0	5.7
	type 2	66.6	62.8
	type 3	30.4	31.5
Intervention	*Antituberculosis chemotherapy plus prednisolone* Prednisolone administered in an oral dose of 0.75 mg/kg of body weight/day initially after 2 to 4 weeks, depending on the therapeutic response as assessed by a progressive reduction of symptoms and radiologic improvement, the dosage was tapered over a 2-week period by 5 mg/dl in all patients Antituberculosis chemotherapy: 6HRZ isoniazid at 8 mg/kg of body weight/day, rifampicin at 10 mg/kg of body weight/day and pyrazinamide at 25 mg/kg of body weight/day for 6 months All patients received 25 mg/kg of body weight/day of pyridoxine		
Comparison	*Antituberculosis chemotherapy plus placebo* Placebo		

	administered in an oral dose of 0.75 mg/kg of body weight/day initially after 2 to 4 weeks, depending on the therapeutic response as assessed by a progressive reduction of symptoms and radiologic improvement, the dosage was tapered over a 2-week period by 5 mg/dl in all patients Antituberculosis chemotherapy: 6HRZ isoniazid at 8 mg/kg of body weight/day, rifampicin at 10 mg/kg of body weight/day and pyrazinamide at 25 mg/kg of body weight/day for 6 months All patients received 25 mg/kg of body weight/day of pyridoxine
Length of follow up	24 weeks
Location	Cape Town, South Africa
Outcomes measures and effect size	**Changes in signs and symptoms – 'morbidity'** A combined index score for morbidity, measured using a visual analogue scale, incorporating well-being, appetite, night sweats, pleuritic chest pain, tiredness, dyspnea and cough Morbidity score (median (range)) at 24 weeks prednisolone group (n = 34) = 0 (0–0) placebo group (n = 36) = 0 (0–0) Median difference[2] = 0 i.e. not statistically significant
	Changes in signs and symptoms – pleural thickening Number of people to with residual pleural thickening, as assessed using a chest x-ray prednisolone group = 17 of 34 placebo group = 18 of 36 OR[3] (95% CI) = 1.00 (0.39 to 2.55)

	i.e. not statistically significant Number of people to with residual pleural thickening, as assessed using a CT scan prednisolone group = 17 of 34 placebo group = 21 of 36 OR[3] (95% CI) = 0.71 (0.28 to 1.84) i.e. not statistically significant Pleural thickening (mean±SD, mm) at 24 weeks, as assessed using a chest x-ray prednisolone group (n = 34) = 2.1±2.7 placebo group (n = 36) = 2.5±3.7 MD[4] (95% CI) = -0.4 (-1.9 to 1.1) i.e. not statistically significant Change in pleural thickening (MD (95% CI), mm) from baseline to 24 weeks, as assessed using a chest x-ray[5] prednisolone group (n = 34) = -7.3 (-9.0 to -5.6) placebo group (n = 36) = -7.9 (-10.1 to -5.7) Difference in change in means[6] = -0.6 Pleural thickening (mean±SD, mm) at 24 weeks, as assessed using a CT scan prednisolone group (n = 34) = 3.0±3.7 placebo group (n = 36) = 4.3±5.1 MD[4] (95% CI) = -1.3 (-3.4 to 0.8)
	Adverse events Number of people to experience an adverse event

	prednisolone group = 4 of 34 placebo group = 3 of 36 OR[3] (95% CI) = 1.47 (0.30 to 7.10) i.e. not statistically significant
Source of funding	No details provided
Comments	

[1] Type 1 = non-specific inflammation of the parietal pleura with no or only a few fibrinous adhesions; type 2 = 'classic' tuberculous pleurisy with an inflamed reddish pleura and multiple greyish-white nodules; type 3 = fibrous inflammation with a thickened parietal pleura and multiple fibrous adhesions and/or loculations

[2] Median difference calculated by reviewer

[3] Odds ratio and 95% confidence interval calculated by reviewer

[4] Mean difference and 95% confidence interval calculated by reviewer

[5] Changes in mean and 95% confidence interval calculated by reviewer

[5] Difference in the changes in mean calculated by reviewer

Abbreviations: CI, confidence intervals; CT, computerised tomography; H, isoniazid; MD, mean difference; OR, odds ratio; R, rifampicin; RCT, randomised controlled trial; SD, standard deviation; Z, pyrazinamide

1.1.9 Singh & Yesikar, 1965

Bibliographic reference	Singh D & Yesikar SS (1965) Role of intrapleural corticosteroids in tuberculous pleural effusion. A clinicotherapeutic trial of 50 cases. Journal of the Indian Medical Association 45(6): 306-9
Study type	Non-randomised controlled trial
Study quality	*Appropriate method of randomisation used?* no

	Allocation concealment used? no *Blinding used?* no *Groups comparable at baseline?* unclear *Groups received the same care apart from the intervention(s) studied?* yes, although details provided are limited *Groups followed up for an equal and appropriate length of time?* unclear *Groups comparable for treatment completion and availability of outcome data?* yes *Study used precise definitions and reliable measures of outcome?* yes *Population studied is the same as the population of interest?* yes *Intervention used is the same as the intervention of interest?* yes, although patients did not receive rifampicin, pyrazinamide and ethambutol but received streptomycin *Have substitute outcomes been used instead of the patient-important outcomes of interest?* recurrence is a substitute for relapse *Analysis followed the intent-to-treat principle?*

	yes
Number of patients	Randomised = 50 dexamethasone group = 30 antituberculosis chemotherapy alone group = 20
Patient characteristics	*Inclusion* Pleural effusion with tuberculous aetiology Typical onset and course of disease Positive Mantoux test
Intervention	*Antituberculosis chemotherapy plus dexamethasone* Dexamethasone 4 mg of dexamethasone injected intrapleurally and the pleural fluid aspirated every 15 days until the puncture was dry Antituberculosis chemotherapy: SH isoniazid at 300 mg/day and streptomycin at 1 g/day All patients received vitamins and haematinics All patients were hospitalised and were at rest
Comparison	*Antituberculosis chemotherapy alone* Antituberculosis chemotherapy: SH isoniazid at 300 mg/day and streptomycin at 1 g/day Half of the patients also underwent aspirations every 15 days until the puncture was dry All patients received vitamins and haematinics All patients were hospitalised and were at rest

Length of follow up	Unclear
Location	Bhopal, India
Outcomes measures and effect size	**Changes in signs and symptoms – effusion** Time (mean, days) taken for complete absorption of pleural effusion dexamethasone group (n = 30) = 23.5 antituberculosis chemotherapy alone group (n = 20) = 71.2 MD[1] = -47.7 Time (mean, days) taken for complete absorption of pleural effusion among those with a large effusion dexamethasone group (n = 9) = 30.0 antituberculosis chemotherapy alone group (n = 4) = 93.8 MD[1] = -63.8 Time (mean, days) taken for complete absorption of pleural effusion among those with a medium effusion dexamethasone group (n = 16) = 22.5 antituberculosis chemotherapy alone group (n = 12) = 72.5 MD[1] = -50.0 Time (mean, days) taken for complete absorption of pleural effusion among those with a small effusion dexamethasone group (n = 5) = 15.0 antituberculosis chemotherapy alone group (n = 4) = 45.0 MD[1] = -30.0
	Changes in signs and symptoms – cough Time (mean, days) to relief of cough

	dexamethasone group (n = 30) = 20.1 antituberculosis chemotherapy alone group (n = 20) = 32.2 MD[1] = -12.1
	Changes in signs and symptoms – shortness of breath Time (mean, days) to relief of shortness of breath dexamethasone group (n = 30) = 3.1 antituberculosis chemotherapy alone group (n = 20) = 15.7 MD[1] = -12.6
	Changes in signs and symptoms – chest pain Time (mean, days) to relief of chest pain dexamethasone group (n = 30) = 6.9 antituberculosis chemotherapy alone group (n = 20) = 20.7 MD[1] = -13.8
	Changes in signs and symptoms – temperature Time (mean, days) to normalisation of temperature dexamethasone group (n = 30) = 9.0 antituberculosis chemotherapy alone group (n = 20) = 28.8 MD[1] = -19.8
	Changes in signs and symptoms – weight Final weight (mean, kg) dexamethasone group (n = 30) = 43.4

	antituberculosis chemotherapy alone group (n = 20) = 41.8 MD[1] = 1.6 Change in mean weight (kg) from baseline to the end of follow-up dexamethasone group (n = 30) = 2.0 antituberculosis chemotherapy alone group (n = 20) = 1.5 MD[1] = 0.5
	Recurrence Number of patients to experience recurrence dexamethasone group = 0 of 30 antituberculosis chemotherapy alone group = 4 of 20 OR[2] (95% CI) = 0.06 (0.00 to 1.19) i.e. not statistically significant
Source of funding	No details provided
Comments	

[1] Mean difference and 95% confidence interval calculated by reviewer

[2] Odds ratio and 95% confidence interval calculated by reviewer

Abbreviations: CI, confidence intervals; H, isoniazid; MD, mean difference; OR, odds ratio; S, streptomycin

TUBERCULOSIS WITH SEVERE BRONCHIAL OBSTRUCTION

1.1.10 Toppet et al, 1990

Bibliographic reference	Toppet M, Malfroot A, Derde MP et al (1990) Corticosteroids in primary tuberculosis with bronchial obstruction. Archives of Disease in Childhood 65: 1222-6
Study type	RCT
Study quality	*Appropriate method of randomisation used?* numbered envelopes *Allocation concealment used?* unclear *Blinding used?* 'open' trial, although examination of bronchoscopy and radiographs blinded *Groups comparable at baseline?* yes *Groups received the same care apart from the intervention(s) studied?* unclear – those receiving steroids were recommended a sodium-restricted diet, potassium glucoconate supplements and gastric protection by aluminium phosphate, but it is unclear if those on antituberculosis chemotherapy alone received these *Groups followed up for an equal and appropriate length of time?* yes *Groups comparable for treatment completion and availability of outcome data?* yes

	Study used precise definitions and reliable measures of outcome? yes *Population studied is the same as the population of interest?* yes *Intervention used is the same as the intervention of interest?* antituberculosis regimens do not use all of or just the 4 standard recommended drugs: lack pyrazinamide *Have substitute outcomes been used instead of the patient-important outcomes of interest?* yes – need for multiple bronchoscopies is a surrogate for changes in signs and symptoms *Analysis followed the intent-to-treat principle?* yes
Number of patients	Randomised = 29 prednisolone group = 15 antituberculosis chemotherapy alone group = 14 Outcome data available for outcomes based on bronchoscopy = 29 prednisolone group = 15 antituberculosis chemotherapy alone group = 14 Outcome data available for outcomes based on radiography = 23 prednisolone group = 13 antituberculosis chemotherapy alone group = 10
Patient characteristics	*Inclusion* Children

Symptomatic tuberculosis with severe bronchial obstruction suspected by radiology and demonstrated by bronchoscopy

A compression of at least 50% of a bronchus

A bronchoscopy score equal or higher than 2, according to the following scoring system:

localisation: trachea = 4; main bronchus = 3; lobar bronchus = 2; segmental bronchus = 1

importance of the obstruction: total or >75% = 4; 50-75% = 2; <50% = 1; no obstruction = 0

Diagnostic criteria

A combination of the following:

recent tuberculin conversion with an induration of at least 10 mm after 48 or 72 hours

clinical signs such as an unexpected course of pulmonary consolidation, long standing unexplained fever or cough

family history of tuberculosis

chest radiographs

bronchoscopy

Exclusion

Patients who already had bronchial fistulisation were not included in this study as the aim was to verify whether fistulisation could be prevented

Meningitis

Miliary tuberculosis

Patients without clinical and radiological abnormalities and negative bacteriology for *M. tuberculosis*

Baseline[1]

	Prednisolone (n = 15)	**Antituberculosis chemotherapy alone group**

<table>
<tr><td></td><td>
<table>
<tr><td></td><td></td><td>(n = 10)</td></tr>
<tr><td>Age (mean±SD (range)), years</td><td>4.3±4.2 (0.3–12)</td><td>5.5±4.2 (0.5–15)</td></tr>
<tr><td>Sex
males, n
females, n</td><td>
11
4</td><td>
8
6</td></tr>
<tr><td>M. tuberculosis culture
positive, n
negative, n</td><td>
9
6</td><td>
9
5</td></tr>
<tr><td>Score on radiology[2] (mean±SD (range))</td><td>4.8±2.2 (3–10)</td><td>3.9±1.4 (2–6)</td></tr>
<tr><td>Score on bronchoscopy[3] (mean±SD (range))</td><td>15.4±6.9 (2–26)</td><td>11.8±5.7 (3–21)</td></tr>
</table>
</td></tr>
<tr><td>Intervention</td><td>Antituberculosis chemotherapy plus prednisolone
Prednisolone (3 to 3.5 months)
started at a daily dose of 2 mg/kg of body weight for 15 days and was progressively decreased to be stopped between 2.5 and 3 months
Antituberculosis chemotherapy: 2HRZE/10HR
10 mg/kg of body weight/day of isoniazid (up to a maximum of 300 mg/day), 15 mg/kg of body weight/day of rifampicin (up to a maximum of 600 mg/day) and 20 mg/kg of body weight/day of ethambutol for 2 months
isoniazid and rifampicin at the same doses for the following 10 months</td></tr>
<tr><td>Comparison</td><td>Antituberculosis chemotherapy alone
Antituberculosis chemotherapy: 2HRZE/10HR</td></tr>
</table>

	10 mg/kg of body weight/day of isoniazid (up to a maximum of 300 mg/day), 15 mg/kg of body weight/day of rifampicin (up to a maximum of 600 mg/day) and 20 mg/kg of body weight/day of ethambutol for 2 months isoniazid and rifampicin at the same doses for the following 10 months
Length of follow up	Full treatment period (12 months)
Location	Brussels, Belgium
Outcomes measures and effect size	**Changes in signs and symptoms – radiological status** Number of patients whose radiological score normalised during treatment prednisolone group = 13 of 15 antituberculosis chemotherapy alone group = 9 of 14 OR[4] (95% CI) = 3.61 (0.57 to 22.90) i.e. not statistically significant Number of patients whose radiological score improved in ≤1 month prednisolone group = 7 of 15 antituberculosis chemotherapy alone group = 0 of 14 **OR[4] (95% CI) = 25.59 (1.29 to 506.48)** **i.e. statistically significant** Number of patients whose radiological score deteriorated during treatment prednisolone group = 2 of 15 antituberculosis chemotherapy alone group = 5 of 14 OR[4] (95% CI) = 0.28 (0.04 to 1.76) i.e. not statistically significant

	Changes in signs and symptoms – bronchial status Change (mean±SD) in bronchoscopy score[3] from baseline to 1 month post-treatment prednisolone group (n = 15) = 12.1±6.9 antituberculosis chemotherapy alone group (n = 14) = 5.9±5.0 **MD[5] (95% CI) = 6.2 (1.83 to 10.57)** **i.e. statistically significant**
	Response to treatment – need for multiple bronchoscopies Number of patients to require >2 bronchoscopies prednisolone group = 1 of 15 antituberculosis chemotherapy alone group = 6 of 14 **OR[4] (95% CI) = 0.10 (0.01 to 0.94)** **i.e. statistically significant**
Source of funding	No details provided
Comments	

[1] Authors provided individual patient data; reviewer summarised for comparison of the 2 groups

[2] Radiological score: size of the adenopathy scored 1 to 3; segmental consolidation or hyperinflation scored 1; lobar consolidation or hyperinflation scored 3; pulmonary consolidation or hyperinflation scored 6

[3] Bronchoscopy score:

localisation: trachea = 4; main bronchus = 3; lobar bronchus = 2; segmental bronchus = 1

importance of the obstruction: total or >75% = 4; 50-75% = 2; <50% = 1; no obstruction = 0

[4] Odds ratio and 95% confidence interval calculated by reviewer

[5] Mean difference and 95% confidence interval calculated by reviewer

Abbreviations: CI, confidence intervals; E, ethambutol; H, isoniazid; OR, odds ratio; R, rifampicin; RCT, randomised controlled trial; SD, standard deviation

CENTRAL NERVOUS SYSTEM TUBERCULOSIS

1.1.11 Chotmongkol et al, 1996

Bibliographic reference	Chotmongkol V, Jitpimolmard S & Thavornpitak Y (1996) Corticosteroid in tuberculous meningitis. Journal of the Medical Association of Thailand 79(2): 83-90
Study type	RCT
Study quality	*Appropriate method of randomisation used?* unclear – patients were randomised by a block size of 4 using coded treatment (A = placebo; B = prednisolone) *Allocation concealment used?* unclear *Blinding used?* double-blind – participants receiving care and individuals administering care were blind to treatment allocation; unclear if investigators were blind to treatment allocation, or to important confounding or prognostic factors *Groups comparable at baseline?* clinical presentations and staging were similar in the intervention and comparator groups at randomisation; however, although not statistically significant, more patients in the prednisolone group (17%) had motor weakness than in the placebo group (3%), and more patients in the prednisolone group (17%) had motor weakness than in the placebo group (10%) additionally, there were more patients with severe (stage 3) disease and fewer patients with less severe (stage 1) disease in the prednisolone group than in the placebo group, although again this was not statistically significant *Groups received the same care apart from the intervention(s) studied?* yes, although details provided are limited *Groups followed up for an equal and appropriate length of time?* yes – 12 months after treatment completion

	Groups comparable for treatment completion and availability of outcome data? yes – 100% in both groups *Study used precise definitions and reliable measures of outcome?* yes, although details provided are limited *Population studied is the same as the population of interest?* yes *Intervention used is the same as the intervention of interest?* antituberculosis regimens do not use all of or just the 4 standard recommended drugs: lack ethambutol and contain streptomycin *Have substitute outcomes been used instead of the patient-important outcomes of interest?* yes – need for additional intervention (response to treatment) is a substitute for treatment success/failure *Analysis followed the intent-to-treat principle?* yes
Number of patients	Randomised = 59 prednisolone group = 29 placebo group = 30
Patient characteristics	*Inclusion* Tuberculous meningitis Aged more than 15 years Negative serologic test for syphilis and HIV *Diagnostic criteria*

According to characteristic clinical features and CSF findings:

lymphocytic meningitis

low glucose level

elevation of protein content

sterile routine bacterial and fungal culture

negative latex agglutination test for bacterial and cryptococcal antigen

negative cytologic study for malignancy

Severity of disease

Classified according to the system of Gordon and Parsons (1972):

stage 1: patients were conscious and rational with meningism but no focal neurological signs or signs of hydrocephalus

stage 2: patients were confused or had focal neurological signs such as squint, hemiparesis or signs of hydrocephalus

stage 3: the patients' mental state could not be assessed because of stupor or delirium, complete hemiplegia or paraplegia

Baseline

	Prednisolone group (n = 29)	**Placebo group** (n = 30)	**p value**
Age (mean±SD), years	42±18.6	39±18.3	0.51
Sex (males), %	55.2	53.3	0.90
Staging			
1, %	10.3	20.0	

		2, %	69.0	66.7		
		3, %	20.7	13.3		
		Headache, %	93.1	96.7	0.61	
		Fever (temperature > 38.0°C), %	93.1	76.7	0.15	
		Stiff neck, %	96.6	96.7	1.00	
		Mental impairment (confusion, stuporous), %	69.0	63.3	0.85	
		Papilloedema, %	24.1	16.7	0.70	
		Cranial nerve palsies, %	24.1	20.0	0.94	
		Decreased vision, %	10.3	10.0		
		Motor weakness (parapesis, hemiparesis), %	17.2	10.0	0.10	
		Other foci of tuberculous infection, %	58.6	43.3	0.36	
		lung, %	51.7	26.7		
		lymph node, %	0.0	10.0		
		spine, %	0.0	3.3		
		larynx, %	3.4	0.0		
		peritoneum, %	3.4	0.0		
		intestine, %	0.0	3.3		
		Abnormal chest x-ray, %	51.7	26.7	0.08	
		Abnormal CT scan of brain (hydrocephalus, lacunar infarction, tuberculoma, brain oedema), %	83.3	84.6	1.0	
		Hyponatraemia (<125 mEq/L), %	20.7	10.0	0.29	

<table>
<tr><td></td><td>
<table>
<tr><td>CSF abnormalities</td><td></td><td></td><td></td></tr>
<tr><td>high opening pressure (>300 mmH2O), %</td><td>51.7</td><td>56.7</td><td>0.90</td></tr>
<tr><td>white blood cell count (/mm3)</td><td></td><td></td><td></td></tr>
<tr><td>mean</td><td>403</td><td>388</td><td>0.80</td></tr>
<tr><td>range</td><td>25–1202</td><td>10–2000</td><td></td></tr>
<tr><td>protein content (mg/dl)</td><td></td><td></td><td></td></tr>
<tr><td>mean</td><td>247.8</td><td>287</td><td>0.67</td></tr>
<tr><td>range</td><td>57–9570</td><td>76–8500</td><td></td></tr>
<tr><td>positive AFB stain, %</td><td>3.4</td><td>0.0</td><td></td></tr>
<tr><td>positive culture for M. tuberculosis, %</td><td>13.8</td><td>3.3</td><td></td></tr>
</table>
</td></tr>
<tr><td>Intervention</td><td>Antituberculosis chemotherapy plus prednisolone
Prednisolone (5 weeks)
60 mg/day taken orally with alum milk in 3 divided doses after meals during the first week
the dose was reduced to 45, 30, 20 and 10 mg/day for the second, third, forth and fifth weeks respectively, then discontinued
Antituberculosis chemotherapy: 2HRZS/4HR
300 mg isoniazid, 600 mg rifampicin (450 mg for those weighing less than 50 kg), 1500 mg pyrazinamide and 750 mg streptomycin for the first 2 months
isoniazid and rifampicin at the same doses for the following 4 months</td></tr>
<tr><td>Comparison</td><td>Antituberculosis chemotherapy plus placebo
Placebo (5 weeks)</td></tr>
</table>

	tablets of identical appearance to the prednisolone 60 mg/day taken orally with alum milk in 3 divided doses after meals during the first week the dose was reduced to 45, 30, 20 and 10 mg/day for the second, third, forth and fifth weeks respectively, then discontinued Antituberculosis chemotherapy: 2HRZS/4HR 300 mg isoniazid, 600 mg rifampicin (450 mg for those weighing less than 50 kg), 1500 mg pyrazinamide and 750 mg streptomycin for the first 2 months isoniazid and rifampicin at the same doses for the following 4 months
Length of follow up	12 months after treatment completion
Location	Khon Kaen, Thailand
Outcomes measures and effect size	**Mortality** Number of deaths prednisolone group = 5 of 29 placebo group = 2 of 30 p = 0.25 OR[1] (95% CI) = 2.92 (0.52 to 16.42) i.e. not statistically significant Stage 1 prednisolone group = 0 of 3 placebo group = 0 of 6 OR[1] (95% CI) = 1.86 (0.03 to 115.45) i.e. not statistically significant

	Stage 2 prednisolone group = 1 of 20 placebo group = 0 of 20 OR[1] (95% CI) = 3.15 (0.12 to 82.17) i.e. not statistically significant Stage 3 prednisolone group = 4 of 6 placebo group = 2 of 4 OR[1] (95% CI) = 2.00 (0.15 to 26.74) i.e. not statistically significant
	Response to treatment – need for additional intervention (ventricular shunting) Number of patients to require ventricular shunting (as indicated by persistent high CSF pressure after 4 weeks of repeated lumbar puncture) prednisolone group = 5 of 29 placebo group = 4 of 30 p = 0.73 OR[1] (95% CI) = 1.35 (0.33 to 5.64) i.e. not statistically significant
	Changes in signs and symptoms – neurological abnormalities during treatment Number of patients to experience neurological abnormalities newly developed during treatment prednisolone group = 2 of 29

	placebo group = 4 of 30 p = 0.67 OR[1] (95% CI) = 0.48 (0.08 to 2.86) i.e. not statistically significant Number of patients to experience urinary retention newly developed during treatment prednisolone group = 1 of 29 placebo group = 1 of 30 OR[1] (95% CI) = 1.04 (0.06 to 17.38) i.e. not statistically significant Number of patients to experience arm weakness newly developed during treatment prednisolone group = 1 of 29 placebo group = 0 of 30 OR[1] (95% CI) = 3.21 (0.13 to 82.07) i.e. not statistically significant Number of patients to experience paraparesis newly developed during treatment prednisolone group = 0 of 29 placebo group = 2 of 30 OR[1] (95% CI) = 0.19 (0.01 to 4.20) i.e. not statistically significant Number of patients to experience hemiparesis newly developed during treatment prednisolone group = 0 of 29

	placebo group = 1 of 30 OR[1] (95% CI) = 0.33 (0.01 to 8.52) i.e. not statistically significant
	Changes in signs and symptoms – neurological abnormalities after treatment Number of patients to experience neurological abnormalities after treatment prednisolone group = 4 of 29 placebo group = 2 of 30 p = 0.42 OR[1] (95% CI) = 2.24 (0.38 to 13.30) i.e. not statistically significant Number of patients to experience decreased vision after treatment prednisolone group = 2 of 29 placebo group = 1 of 30 OR[1] (95% CI) = 2.15 (0.18 to 25.07) i.e. not statistically significant Number of patients to experience spastic paraparesis after treatment prednisolone group = 1 of 29 placebo group = 1 of 30 OR[1] (95% CI) = 1.04 (0.06 to 17.38) i.e. not statistically significant Number of patients to experience hemiparesis after treatment

	prednisolone group = 1 of 29 placebo group = 0 of 30 OR[1] (95% CI) = 3.21 (0.13 to 82.07) i.e. not statistically significant
	Changes in signs and symptoms - headache Time (mean, days) until disappearance of headache prednisolone group (n = 29) = 15.9 placebo group (n = 30) = 13.3 p = 0.61 MD[2] = 2.6
	Changes in signs and symptoms - fever Time (mean (range), days) until normal body temperature prednisolone group (n = 29) = 5.6 (1 – 27) placebo group (n = 30) = 9.3 (2 – 21) p = 0.06 MD[2] = -3.7
	Recurrence Number of patients to experience recurrence of meningitis during follow-up prednisolone group = 0 of 29 placebo group = 0 of 30 OR[1] (95% CI) = 1.03 (0.02 to 53.83)

	i.e. not statistically significant
	Adverse events - gastrointestinal bleeding Number of patients to experience gastrointestinal bleeding prednisolone group = 0 of 29 placebo group = 0 of 30 OR[1] (95% CI) = 1.03 (0.02 to 53.83) i.e. not statistically significant
	Adverse events - hyperglycaemia Number of patients to experience hyperglycaemia prednisolone group = 0 of 29 placebo group = 0 of 30 OR[1] (95% CI) = 1.03 (0.02 to 53.83) i.e. not statistically significant
Source of funding	Tablets of prednisolone and placebo were provided by Siam Pharmaceutical Co. Ltd.
Comments	

[1] Odds ratio and 95% confidence interval calculated by reviewer

[2] Mean difference calculated by reviewer

Abbreviations: AFB, acid-fast bacilli; CI, confidence intervals; CSF, cerebrospinal fluid; CT, computerised tomography; H, isoniazid; HIV, human immunodeficiency virus; MD, mean difference; OR, odds ratio; R, rifampicin; RCT, randomised controlled trial; S, streptomycin; SD, standard deviation; TB, tuberculosis; Z, pyrazinamide

1.1.12 Girgis et al, 1983

Bibliographic reference	Girgis NI, Farid Z, Hanna LS (1983) The use of dexamethasone in preventing ocular complications in tuberculous meningitis. Transactions of the Royal Society of Tropical Medicine and Hygiene 77(5): 658-9
Study type	Non-randomised controlled trial
Study quality	*Appropriate method of randomisation used?* no – allocation was not randomised, rather patients were alternately assigned to receive antituberculosis chemotherapy plus dexamethasone or antituberculosis chemotherapy alone *Allocation concealment used?* no *Blinding used?* unclear *Groups comparable at baseline?* authors state that groups were comparable with respect to age, sex and disease severity on admission to hospital; however, although not statistically significant, more patients in the dexamethasone group (32/70) were comatose on admission than in the antituberculosis chemotherapy alone group (41/66) – that is, the condition of those in the dexamethasone group could be considered to be more severe *Groups received the same care apart from the intervention(s) studied?* yes, although details provided are limited *Groups followed up for an equal and appropriate length of time?* unclear *Groups comparable for treatment completion and availability of outcome data?* unclear *Study used precise definitions and reliable measures of outcome?*

<table>
<tr><td></td><td>yes, although details provided are limited

Population studied is the same as the population of interest?

yes

Intervention used is the same as the intervention of interest?

antituberculosis regimens do not use all of or just the 4 standard recommended drugs: lack rifampicin and pyrazinamide, but contain streptomycin

Have substitute outcomes been used instead of the patient-important outcomes of interest?

no</td></tr>
<tr><td>Number of patients</td><td>Included = 136

dexamethasone group = 66

antituberculosis chemotherapy alone group = 70</td></tr>
<tr><td>Patient characteristics</td><td>Inclusion

Tuberculous meningitis

Diagnostic criteria

Isolation of tubercle bacilli from the CSF, or a CSF findings consistent with tuberculous meningitis (increased protein, low glucose, and lymphocytotic pleocytosis)

Baseline
<table>
<tr><th></th><th>Dexamethasone group
(n = 66)</th><th>Antituberculosis chemotherapy alone group
(n = 70)</th></tr>
<tr><td>Sex
males, %</td><td>
45.5</td><td>
54.3</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><td></td><td>
<table>
<tr><td>females, %</td><td>54.5</td><td>45.7</td></tr>
<tr><td>Age (mean (range)), years</td><td>14.6 (0.5 – 52)</td><td>13.6 (0.6 – 42)</td></tr>
<tr><td>CSF positive for tubercle bacilli, %</td><td>45.5</td><td>48.6</td></tr>
<tr><td>Duration of symptoms prior to admission (mean (range)), days</td><td>27.8 (6 – 120)</td><td>25.5 (5 – 105)</td></tr>
<tr><td>Clinical condition on admission
alert, %
drowsy, %
comatose, %</td><td>
3.0
34.8
62.1</td><td>
7.1
47.1
45.7</td></tr>
</table>
</td></tr>
<tr><td>Intervention</td><td>Antituberculosis chemotherapy plus dexamethasone
Dexamethasone (3 weeks)
8 to 12 mg/day
Antituberculosis chemotherapy: 1.5HSE/22.5HE
10 mg/kg of body weight/day isoniazid, 25 mg/kg of body weight/day streptomycin and 25 mg/kg of body weight/day ethambutol for the first 60 days
10 mg/kg of body weight/day isoniazid and 25 mg/kg of body weight/ day ethambutol for the remainder of the 2-year treatment period</td></tr>
<tr><td>Comparison</td><td>Antituberculosis chemotherapy alone
Antituberculosis chemotherapy: 1.5HSE/22.5HE
10 mg/kg of body weight/day isoniazid, 25 mg/kg of body weight/day streptomycin and 25 mg/kg of body weight/day ethambutol for the first 60 days
10 mg/kg of body weight/day isoniazid and 25 mg/kg of body weight/ day ethambutol for the remainder of the 2-year</td></tr>
</table>

	treatment period
Length of follow up	Unclear
Location	Cairo, Egypt
Outcomes measures and effect size	**Mortality** Number of deaths dexamethasone group = 39 of 66 antituberculosis chemotherapy alone group = 42 of 70 OR[1] (95% CI) = 0.96 (0.49 to 1.91) i.e. not statistically significant Alert on admission dexamethasone group = 0 of 2 antituberculosis chemotherapy alone group = 2 of 5 OR[1] (95% CI) = 0.28 (0.01 to 8.76) i.e. not statistically significant Drowsy on admission dexamethasone group = 8 of 23 antituberculosis chemotherapy alone group = 14 of 33 OR[1] (95% CI) = 0.72 (0.24 to 2.18) i.e. not statistically significant Comatose admission dexamethasone group = 31 of 41

	antituberculosis chemotherapy alone group = 26 of 32 OR[1] (95% CI) = 0.72 (0.23 to 2.23) i.e. not statistically significant CSF positive for tubercle bacilli dexamethasone group = 19 of 30 antituberculosis chemotherapy alone group = 21 of 34 OR[1] (95% CI) = 1.07 (0.39 to 2.95) i.e. not statistically significant
	Adverse events – ocular complications Number of patients with ocular complications dexamethasone group = 2 of 66 antituberculosis chemotherapy alone group = 7 of 70 OR[1] (95% CI) = 0.28 (0.06 to 1.41) i.e. not statistically significant Number of patients with CSF positive for tubercle bacilli with ocular complications dexamethasone group = 2 of 30 antituberculosis chemotherapy alone group = 4 of 34 OR[1] (95% CI) = 2.46 (0.42 to 14.52) i.e. not statistically significant
Source of funding	No details provided
Comments	

[1] Odds ratio and 95% confidence interval calculated by reviewer

Abbreviations: CI, confidence intervals; CSF, cerebrospinal fluid; E, ethambutol H, isoniazid; OR, odds ratio; RCT, randomised controlled trial; S, streptomycin; TB, tuberculosis

1.1.13 Girgis et al, 1991

Bibliographic reference	Girgis NI, Farid Z, Kilpatrick ME (1991) Dexamethasone adjunctive treatment for tuberculous meningitis. Pediatric Infectious Disease Journal 10(3): 179-83
Study type	RCT
Study quality	*Appropriate method of randomisation used?* yes – number randomisation chart *Allocation concealment used?* unclear *Blinding used?* unclear *Groups comparable at baseline?* yes *Groups received the same care apart from the intervention(s) studied?* yes *Groups followed up for an equal and appropriate length of time?* yes *Groups comparable for treatment completion and availability of outcome data?* limited data available for the incidence of neurologic abnormalities due to a high rate of mortality, though the loss to follow-up was similar in the 2 groups (dexamethasone = 72 of 145; antituberculosis chemotherapy alone = 79 of 135)

	Study used precise definitions and reliable measures of outcome? yes, although details provided are limited *Population studied is the same as the population of interest?* yes *Intervention used is the same as the intervention of interest?* antituberculosis regimens do not use all of or just the 4 standard recommended drugs: lack rifampicin and pyrazinamide, but contain streptomycin *Have substitute outcomes been used instead of the patient-important outcomes of interest?* no *Analysis followed the intent-to-treat principle?* yes
Number of patients	Included = 280 dexamethasone group = 145 antituberculosis chemotherapy alone group = 135
Patient characteristics	*Inclusion* Tuberculous meningitis *Diagnostic criteria* Clinical history Signs and symptoms compatible with tuberculous meningitis: low grade fever severe progressive headache

vomiting

generalised weakness

diplopia

cranial nerve affections

deterioration of mental alertness

duration of illness more than 30 days

comparison of results from the first and second CSF examinations

poor response to antibacterial therapy (250,000 units/kg of body weight/day of penicillin or 160 mg/kg of body weight/day of ampicillin plus 100 mg/kg of body weight/day of chloramphenicol) for 48 hours

Baseline

	Dexamethasone group (n = 145)		**Antituberculosis chemotherapy alone group** (n = 135)	
	CSF culture-positive (n = 75)	**CSF culture-negative** (n = 70)	**CSF culture-positive** (n = 85)	**CSF culture-negative** (n = 50)
Sex				
male, n	38	43	46	31
female, n	37	27	39	19
Age				
(median), years	12	6	6	16
<1 year, n	4	8	5	5

		1–5 years, n	19	27	25	11
		6–15 years, n	23	11	21	7
		16–25 years, n	15	7	12	14
		>25 years, n	14	17	22	13
		Duration of symptoms prior to hospitalisation				
		<14 days, n	13	20	21	20
		15–28 days, n	49	24	46	14
		29–43 days, n	5	18	6	7
		>43 days, n	8	8	12	9
		State of consciousness on admission				
		alert, n	4	2	4	1
		drowsy, n	27	15	35	10
		comatose, n	44	53	46	39
		Cranial nerve afflictions, n	41	59	37	46
		Pupillary abnormalities, n	65	63	70	48
		Fundus changes, n	2	5	2	4
		Hemiparesis, n	1	2	2	3
		Hydrocephalus, n	1	2	0	1
Intervention	*Antituberculosis chemotherapy plus dexamethasone*					

	Dexamethasone (3 weeks) 12 mg/day in adults, and 8 mg/day in children weighing less than 25 kg Antituberculosis chemotherapy: 1.5HSE/22.5HE 10 mg/kg of body weight/day isoniazid (to a maximum of 600 mg), 25 mg/kg of body weight/day streptomycin (to a maximum of 1000 mg) and 25 mg/kg of body weight/day ethambutol (to a maximum of 1200 mg) for the first 6 weeks 10 mg/kg of body weight/day isoniazid (to a maximum of 600 mg) and 15 mg/kg of body weight/day ethambutol for the remainder of the 2-year treatment period In patients with permanent CT-confirmed hydrocephalus, ventriculoperitoneal shunts were performed
Comparison	*Antituberculosis chemotherapy alone* Antituberculosis chemotherapy: 1.5HSE/22.5HE 10 mg/kg of body weight/day isoniazid (to a maximum of 600 mg), 25 mg/kg of body weight/day streptomycin (to a maximum of 1000 mg) and 25 mg/kg of body weight/day ethambutol (to a maximum of 1200 mg) for the first 6 weeks 10 mg/kg of body weight/day isoniazid (to a maximum of 600 mg) and 15 mg/kg of body weight/day ethambutol for the remainder of the 2-year treatment period In patients with permanent CT-confirmed hydrocephalus, ventriculoperitoneal shunts were performed
Length of follow up	Full treatment period
Location	Cairo, Egypt
Outcomes measures and effect size	**Mortality** Number of deaths dexamethasone group = 72 of 145 antituberculosis chemotherapy alone group = 79 of 135 OR[1] (95% CI) = 0.70 (0.44 to 1.12) i.e. not statistically significant

	CSF positive for tubercle bacilli dexamethasone group = 32 of 75 antituberculosis chemotherapy alone group = 50 of 85 **OR[1] (95% CI) = 0.52 (0.28 to 0.98)** **i.e. statistically significant** CSF negative for tubercle bacilli dexamethasone group = 40 of 70 antituberculosis chemotherapy alone group = 29 of 50 OR[1] (95% CI) = 0.97 (0.46 to 2.01) i.e. not statistically significant Alert on admission dexamethasone group = 0 of 6 antituberculosis chemotherapy alone group = 2 of 5 OR[1] (95% CI) = 0.11 (0.00 to 2.93) i.e. not statistically significant Drowsy on admission dexamethasone group = 10 of 42 antituberculosis chemotherapy alone group = 18 of 45 OR[1] (95% CI) = 0.47 (0.19 to 1.18) i.e. not statistically significant Comatose admission

	dexamethasone group = 62 of 97 antituberculosis chemotherapy alone group = 59 of 85 OR[1] (95% CI) = 0.78 (0.42 to 1.45) i.e. not statistically significant
	Changes in signs and symptoms – neurologic abnormalities (developed during treatment) Number of patients to develop neurologic abnormalities (fundus, hemiparesis or hydrocephalus) during treatment dexamethasone group = 8 of 145 antituberculosis chemotherapy alone group = 15 of 135 OR[1] (95% CI) = 0.47 (0.19 to 1.14) i.e. not statistically significant CSF positive for tubercle bacilli dexamethasone group = 4 of 75 antituberculosis chemotherapy alone group = 10 of 85 OR[1] (95% CI) = 0.42 (0.13 to 1.41) i.e. not statistically significant CSF negative for tubercle bacilli dexamethasone group = 4 of 70 antituberculosis chemotherapy alone group = 5 of 50 OR[1] (95% CI) = 0.67 (0.17 to 2.60) i.e. not statistically significant
	Changes in signs and symptoms – neurologic abnormalities (permanent residual sequelae)

	Number of patients to with permanent residual neurologic abnormalities (fundus, hemiparesis or hydrocephalus) dexamethasone group = 14 of 145 antituberculosis chemotherapy alone group = 27 of 135 **OR[1] (95% CI) = 0.43 (0.21 to 0.86)** **i.e. statistically significant** CSF positive for tubercle bacilli dexamethasone group = 6 of 75 antituberculosis chemotherapy alone group = 13 of 85 OR[1] (95% CI) = 0.48 (0.17 to 1.34) i.e. not statistically significant CSF negative for tubercle bacilli dexamethasone group = 8 of 70 antituberculosis chemotherapy alone group = 14 of 50 **OR[1] (95% CI) = 0.33 (0.13 to 0.87)** **i.e. statistically significant**
	Changes in signs and symptoms – fever Time (mean±SD, days) to become afebrile (defined as a temperature of <37.5°C) (patients who were CSF positive for tubercle bacilli on admission) dexamethasone group (n = 75) = 20±13 antituberculosis chemotherapy alone group (n = 85) = 23±12 MD[2] (95% CI) = -3 (-6.9 to 0.9)

	i.e. not statistically significant
	Changes in signs and symptoms – responsiveness Time (mean±SD, days) to become fully alert (defined as adult patients able to respond and answer complicated questions correctly, and infants knowing their mothers, responding to voice or noise and able to feed properly) (patients who were CSF positive for tubercle bacilli on admission) dexamethasone group (n = 75) = 35±33 antituberculosis chemotherapy alone group (n = 85) = 31±23 MD[2] (95% CI) = 4 (-4.9 to 12.9) i.e. not statistically significant
Source of funding	Supported by the United States Navy Department, the Department of Defence, the United States Government and the Egyptian Ministry of Health
Comments	

[1] Odds ratio and 95% confidence interval calculated by reviewer

[2] Mean difference and 95% confidence interval calculated by reviewer

Abbreviations: CI, confidence intervals; CSF, cerebrospinal fluid; CT, computerised tomography; E, ethambutol H, isoniazid; MD, mean difference; OR, odds ratio; RCT, randomised controlled trial; S, streptomycin; SD, standard deviation; TB, tuberculosis

1.1.14 Malhotra et al, 2009

Bibliographic reference	Malhotra HS, Garg RK, Singh MK et al (2009) Corticosteroids (dexamethasone *versus* intravenous methyl prednisolone) in patients with tuberculous meningitis. Annals of Tropical Medicine & Parasitology 103(7): 625-34
Study type	RCT
Study quality	*Appropriate method of randomisation used?* yes – computer-generated randomisation sheet *Allocation concealment used?*

	unclear *Blinding used?* no *Groups comparable at baseline?* yes *Groups received the same care apart from the intervention(s) studied?* yes *Groups followed up for an equal and appropriate length of time?* yes *Groups comparable for treatment completion and availability of outcome data?* yes *Study used precise definitions and reliable measures of outcome?* yes *Population studied is the same as the population of interest?* yes *Intervention used is the same as the intervention of interest?* yes, although some patients received streptomycin instead of ethambutol during the initial phase of treatment *Have substitute outcomes been used instead of the patient-important outcomes of interest?* no *Analysis followed the intent-to-treat principle?* yes

Number of patients	Randomised = 97 dexamethasone group = 32 methylprednisolone group = 33 antituberculosis chemotherapy alone group = 32 Outcome data available for = 91 dexamethasone group = 31 methylprednisolone group = 30 antituberculosis chemotherapy alone group = 30
Patient characteristics	*Inclusion* Tuberculous meningitis Aged >14 years *Diagnostic criteria* Based on the results of clinical and radiological examination, the evaluation of cell types and numbers, and protein and glucose concentrations in the CSF The essential clinical indicator was the presence of a meningitic syndrome, as defined by the presence of headache vomiting and fever In the CSF samples, a predominantly lymphocytotic pleocytosis and an elevated protein concentration were taken as further evidence tuberculous meningitis 'Definite' meningitis = acid-fast bacilli detected in the CSF; contrast-enhanced CT often demonstrated the presence of exudates, hydrocephalus, tuberculoma and infarction, singly or in combination 'Probable' meningitis = suspected active pulmonary TB, as indicated by a chest x-ray; acid-fast bacilli in any specimen other than CSF; and/or clinical evidence of other extrapulmonary tuberculosis 'Possible' meningitis = at least 4 of the following:

history of tuberculosis

predominance of lymphocytes in the CSF

illness lasting >5 days

a ratio of CSF glucose concentration:plasma glucose concentration of <0.5

altered consciousness

yellow CSF

focal neurological signs

Drug susceptibility was not tested

Severity of disease

Classified according to the system of the British Medical Research Council:

stage 1: no definite neurological symptoms; scoring 15 on the Glasgow coma scale

stage 2: signs of meningeal irritation with slight or no clouding of sensorium and minor neurological deficit or no deficit; scoring 11–14 on the Glasgow coma scale

stage 3: severe clouding of sensorium, convulsions, focal neurological deficit and involuntary movements; scoring ≤10 on the Glasgow coma scale

Exclusion

HIV infection

Contraindication of corticosteroids

Previous use of antituberculosis chemotherapy and/or corticosteroids

Evidence of a brain abscess or tumour – e.g. an intracranial space-occupying lesion visible by CT

Baseline

	Dexamethasone	**Methylprednisolone**	**Antituberculosis**

				chemotherapy alone
	Sex			
	male, n	15	14	14
	female, n	16	16	16
	Age (mean (range)), years	31.97 (15–66)	30.00 (15–67)	32.87 (15–70)
	Duration of illness (mean (range)), days	56.13 (7–240)	35.17 (6–180)	60.77 (7–200)
	Glasgow coma scale score (median (range))	15 (8–15)	14.5 (5–15)	15 (8–15)
	Severity of disease			
	stage 1, n	7	7	7
	stage 2, n	18	17	18
	stage 3, n	6	6	5
	History of tuberculosis, n	4	6	7
	Fever, n	27	29	27
	Headache, n	27	27	25
	Vomiting, n	22	17	17
	Seizures, n	7	11	7
	Visual symptoms, n	15	14	16
	Altered sensorium, n	12	15	12
	Cranial nerve palsies, n	12	11	9
	Focal deficits, n	5	4	4

	Visual impairment, n	11	9	8
	Miliary shadow on chest x-ray, n	2	5	3
	Parenchymal shadow on chest x-ray, n	1	0	3
	Pleural effusion on chest x-ray, n	0	2	1
	Basal exudates on CT scan of brain, n	13	11	10
	Hydrocephalus on CT scan of brain, n	10	3	7
	Infarction on CT scan of brain, n	5	4	3
	Culture-positive for *M. tuberculosis*, n	1	1	1
	PCR-positive for *M. tuberculosis*, n	5	8	3
Intervention 1	*Antituberculosis chemotherapy plus dexamethasone* Dexamethasone (4 weeks) 0.4, 0.3, 0.2 and 0.1 mg/kg of bodyweight/day during weeks 1, 2, 3 and 4, respectively Antituberculosis chemotherapy: 2HRZE/7HR or 2HRZS/7HR 10 mg/kg of body weight/day isoniazid, 15 mg/kg of body weight/day rifampicin, 30 mg/kg of body weight/day pyrazinamide, and 15 mg/kg of body weight/day streptomycin or 20 mg/kg of body weight/day ethambutol for the first 2 months 10 mg/kg of body weight/day isoniazid and 15 mg/kg of body weight/day rifampicin for the following 7 months Appropriate symptomatic treatments – intravenous fluids, mannitol, anti-epileptic drugs and/or analgesics – were supplied, as required			
Intervention 2	*Antituberculosis chemotherapy plus methylprednisolone* Methylprednisolone (5 days)			

	daily doses of 1 g for patients weighing >50 kg, or 20 mg/kg for lighter patients, for 5 days Antituberculosis chemotherapy: 2HRZE/7HR or 2HRZS/7HR 10 mg/kg of body weight/day isoniazid, 15 mg/kg of body weight/day rifampicin, 30 mg/kg of body weight/day pyrazinamide, and 15 mg/kg of body weight/day streptomycin or 20 mg/kg of body weight/day ethambutol for the first 2 months 10 mg/kg of body weight/day isoniazid and 15 mg/kg of body weight/day rifampicin for the following 7 months Appropriate symptomatic treatments – intravenous fluids, mannitol, anti-epileptic drugs and/or analgesics – were supplied, as required
Comparison	*Antituberculosis chemotherapy alone* Antituberculosis chemotherapy: 2HRZE/7HR or 2HRZS/7HR 10 mg/kg of body weight/day isoniazid, 15 mg/kg of body weight/day rifampicin, 30 mg/kg of body weight/day pyrazinamide, and 15 mg/kg of body weight/day streptomycin or 20 mg/kg of body weight/day ethambutol for the first 2 months 10 mg/kg of body weight/day isoniazid and 15 mg/kg of body weight/day rifampicin for the following 7 months Appropriate symptomatic treatments – intravenous fluids, mannitol, anti-epileptic drugs and/or analgesics – were supplied, as required
Length of follow up	10 months after treatment initiation
Location	Lucknow, India
Outcomes measures and effect size	**Mortality** Number of deaths after 6 months of treatment dexamethasone group = 8 of 32 methylprednisolone group = 9 of 33 antituberculosis chemotherapy alone group = 13 of 32

	Any corticosteroid vs *antituberculosis chemotherapy alone*[1] OR (95% CI) = 0.52 (0.21 to 1.27) i.e. not statistically significant *Dexamethasone* vs *antituberculosis chemotherapy alone*[2] OR (95% CI) = 0.56 (0.15 to 2.02) i.e. not statistically significant *Methylprednisolone* vs *antituberculosis chemotherapy alone*[2] OR (95% CI) = 0.48 (0.14 to 1.68) i.e. not statistically significant Stage 1 dexamethasone group = 0 of 7 methylprednisolone group = 0 of 7 antituberculosis chemotherapy alone group = 1 of 7 *Any corticosteroid* vs *antituberculosis chemotherapy alone*[1] OR (95% CI) = 0.15 (0.01 to 4.18) i.e. not statistically significant Stage 2 dexamethasone group = 5 of 18 methylprednisolone group = 6 of 17 antituberculosis chemotherapy alone group = 8 of 18 *Any corticosteroid* vs *antituberculosis chemotherapy alone*[1]

	OR (95% CI) = 0.57 (0.18 to 1.85) i.e. not statistically significant Stage 3 dexamethasone group = 3 of 6 methylprednisolone group = 3 of 6 antituberculosis chemotherapy alone group = 4 of 5 *Any corticosteroid* vs *antituberculosis chemotherapy alone*[1] OR (95% CI) = 0.25 (0.02 to 2.94) i.e. not statistically significant
	Changes in signs and symptoms – disability Assessed using a modified Rankin scale: score of 0 = no symptoms at all score of 1 = no significant disability despite the presence of symptoms, with the subject able to carry out all their usual duties and activities score of 2 = slight disability, with the subject unable to carry out all their previous activities, but able to look after their own affairs without assistance score of 3 = moderate disability, with the subject requiring help but able to walk without assistance score of 4 = moderately severe disability, with the subject unable to walk without assistance and unable to attend to own bodily needs without assistance score of 5 = severe disability, with the subject bedridden, incontinent and requiring constant nursing care and attention Final scores: 0 = good outcome

	1–2 = intermediate disability 3–5 = severe disability Number of patients to experience severe disability after 6 months of treatment dexamethasone group = 5 of 32 methylprednisolone group = 6 of 33 antituberculosis chemotherapy alone group = 5 of 32 *Any corticosteroid* vs *antituberculosis chemotherapy alone*[1] OR (95% CI) = 1.10 (0.35 to 3.49) i.e. not statistically significant *Dexamethasone* vs *antituberculosis chemotherapy alone*[2] OR (95% CI) = 1.30 (0.22 to 7.55) i.e. not statistically significant *Methylprednisolone* vs *antituberculosis chemotherapy alone*[2] OR (95% CI) = 0.96 (0.21 to 4.47) i.e. not statistically significant Severe disability among patients defined as stage 1 at baseline dexamethasone group = 1 of 7 methylprednisolone group = 1 of 7 antituberculosis chemotherapy alone group = 1 of 7 *Any corticosteroid* vs *antituberculosis chemotherapy alone*[1] OR (95% CI) = 1.00 (0.07 to 13.37)

	i.e. not statistically significant Severe disability among patients defined as stage 2 at baseline dexamethasone group = 3 of 18 methylprednisolone group = 3 of 17 antituberculosis chemotherapy alone group = 3 of 18 *Any corticosteroid* vs *antituberculosis chemotherapy alone*[1] OR (95% CI) = 1.03 (0.23 to 4.73) i.e. not statistically significant Severe disability among patients defined as stage 3 at baseline dexamethasone group = 1 of 6 methylprednisolone group = 2 of 6 antituberculosis chemotherapy alone group = 1 of 5 *Any corticosteroid* vs *antituberculosis chemotherapy alone*[1] OR (95% CI) = 1.22 (0.10 to 17.10) i.e. not statistically significant Number of patients to experience intermediate disability after 6 months of treatment dexamethasone group = 3 of 32 methylprednisolone group = 0 of 33 antituberculosis chemotherapy alone group = 4 of 32 *Any corticosteroid* vs *antituberculosis chemotherapy alone*[1] OR (95% CI) = 0.34 (0.07 to 1.62)

	i.e. not statistically significant *Dexamethasone* vs *antituberculosis chemotherapy alone*[2] OR (95% CI) = 0.72 (0.11 to 4.84) i.e. not statistically significant *Methylprednisolone* vs *antituberculosis chemotherapy alone*[2] OR (95% CI) = 0.09 (0.00 to 1.92) i.e. not statistically significant Number of patients with a good outcome after 6 months of treatment dexamethasone group = 15 of 32 methylprednisolone group = 15 of 33 antituberculosis chemotherapy alone group = 8 of 32 *Any corticosteroid* vs *antituberculosis chemotherapy alone*[1] **OR (95% CI) = 2.57 (1.01 to 6.56)** **i.e. statistically significant** *Dexamethasone* vs *antituberculosis chemotherapy alone*[2] OR (95% CI) = 2.65 (0.70 to 9.99) i.e. not statistically significant *Methylprednisolone* vs *antituberculosis chemotherapy alone*[2] OR (95% CI) = 2.50 (0.67 to 9.39) i.e. not statistically significant
	Adverse events - hepatic

	Number of patients to experience clinical or subclinical hepatitis dexamethasone group = 5 of 32 methylprednisolone group = 7 of 33 antituberculosis chemotherapy alone group = 8 of 32 *Any corticosteroid* vs *antituberculosis chemotherapy alone*[1] OR (95% CI) = 0.68 (0.25 to 1.88) i.e. not statistically significant *Dexamethasone* vs *antituberculosis chemotherapy alone*[2] OR (95% CI) = 0.56 (0.13 to 2.44) i.e. not statistically significant *Methylprednisolone* vs *antituberculosis chemotherapy alone*[2] OR (95% CI) = 0.81 (0.20 to 3.30) i.e. not statistically significant Number of patients to experience clinical hepatitis dexamethasone group = 1 of 32 methylprednisolone group = 2 of 33 antituberculosis chemotherapy alone group = 2 of 32 *Any corticosteroid* vs *antituberculosis chemotherapy alone*[1] OR (95% CI) = 0.73 (0.12 to 4.58) i.e. not statistically significant *Dexamethasone* vs *antituberculosis chemotherapy alone*[2]

	OR (95% CI) = 0.48 (0.03 to 8.28) i.e. not statistically significant *Methylprednisolone* vs *antituberculosis chemotherapy alone*[2] OR (95% CI) = 0.97 (0.08 to 11.54) i.e. not statistically significant
	Adverse events – gastrointestinal bleeding Number of patients to experience gastrointestinal bleeding dexamethasone group = 4 of 32 methylprednisolone group = 2 of 33 antituberculosis chemotherapy alone group = 1 of 32 *Any corticosteroid* vs *antituberculosis chemotherapy alone*[1] OR (95% CI) = 3.15 (0.36 to 27.37) i.e. not statistically significant *Dexamethasone* vs *antituberculosis chemotherapy alone*[2] OR (95% CI) = 5.21 (0.26 to 103.00) i.e. not statistically significant *Methylprednisolone* vs *antituberculosis chemotherapy alone*[2] OR (95% CI) = 0.97 (0.08 to 11.54) i.e. not statistically significant
	Adverse events – paradoxical tuberculoma Number of patients to experience paradoxical tuberculoma

	dexamethasone group = 2 of 32 methylprednisolone group = 1 of 33 antituberculosis chemotherapy alone group = 5 of 32 *Any corticosteroid* vs *antituberculosis chemotherapy alone*[1] OR (95% CI) = 0.26 (0.06 to 1.17) i.e. not statistically significant *Dexamethasone* vs *antituberculosis chemotherapy alone*[2] OR (95% CI) = 0.47 (0.06 to 3.66) i.e. not statistically significant *Methylprednisolone* vs *antituberculosis chemotherapy alone*[2] OR (95% CI) = 0.14 (0.01 to 1.42) i.e. not statistically significant
Source of funding	No details provided
Comments	

[1] Pooled odds ratio, combining the data for the dexamethasone and methylprednisolone arms into a single 'corticosteroid' arm, and 95% confidence interval calculated by reviewer

[2] Odds ratio and 95% confidence interval calculated by reviewer; data for the control group (received antituberculosis chemotherapy alone) was divided in half to allow 2 pairwise comparisons of dexamethasone plus antituberculosis chemotherapy *versus* antituberculosis chemotherapy alone and methylprednisolone plus antituberculosis chemotherapy *versus* antituberculosis chemotherapy alone

[3] Pooled mean difference, combining the data for the dexamethasone and methylprednisolone arms into a single 'corticosteroid' arm, calculated by reviewer

[4] Mean difference calculated by reviewer; data for the control group (received antituberculosis chemotherapy alone) was divided in half to allow 2 pairwise comparisons of dexamethasone plus antituberculosis chemotherapy *versus* antituberculosis chemotherapy alone and

methylprednisolone plus antituberculosis chemotherapy *versus* antituberculosis chemotherapy alone Abbreviations: CI, confidence intervals; CSF, cerebrospinal fluid; CT, computerised tomography; E, ethambutol H, isoniazid; MD, mean difference; OR, odds ratio; PCR, polymerase chain reaction; RCT, randomised controlled trial; S, streptomycin; SD, standard deviation; TB, tuberculosis; Z, pyrazinamide

1.1.15 O'Toole et al, 1969

Bibliographic reference	O'Toole RD, Thornton GF, Mukherjee MK et al (1969) Dexamethasone in tuberculous meningitis. Relationship of cerebrospinal fluid effects to therapeutic efficacy. Annals of Internal Medicine 70(1): 39-48
Study type	RCT
Study quality	*Appropriate method of randomisation used?* yes – block randomisation using coded medication *Allocation concealment used?* unclear *Blinding used?* double-blind *Groups comparable at baseline?* yes, although details provided are limited *Groups received the same care apart from the intervention(s) studied?* yes, although details provided are limited *Groups followed up for an equal and appropriate length of time?* unclear *Groups comparable for treatment completion and availability of outcome data?* unclear

	Study used precise definitions and reliable measures of outcome? yes *Population studied is the same as the population of interest?* yes *Intervention used is the same as the intervention of interest?* antituberculosis regimens do not use all of or just the 4 standard recommended drugs: lack rifampicin, pyrazinamide and ethambutol, but contain streptomycin *Have substitute outcomes been used instead of the patient-important outcomes of interest?* no *Analysis followed the intent-to-treat principle?* unclear
Number of patients	Outcome data available for = 23 dexamethasone group = 11 placebo group = 12
Patient characteristics	*Inclusion* Tuberculous meningitis (only those patients presenting with short histories or acute signs and symptoms mimicking pyrogenic meningitis were admitted to the hospital since hospital policy is to refer tuberculous meningitis to other institutions) Moderately advanced or severe disease *Severity of disease* Classified according to the system of the British Medical Research Council: stage 1: mild cases; without altered consciousness or focal neurologic signs

stage 2: moderately advanced cases; altered consciousness; not comatose; moderate neurologic deficits, such as single cranial nerve palsies, parapesis and hemiparesis

stage 3: severe cases; comatose patients; multiple cranial nerve palsies; hemiplegia and/or paraplegia

Baseline

	Dexamethasone group (n = 11)	**Placebo group** (n = 12
Age, years		
<2, n	2	3
2 to 45, n	8	9
>45, n	1	0
Severity of disease		
stage 1, n	1	0
stage 2, n	6	8
stage 3, n	4	4
Culture-positive CSF, n	8	6

Intervention

Antituberculosis chemotherapy plus dexamethasone

Dexamethasone (4 weeks)

adults received 2.25 mg parenterally every 6 hours during the first week; the dose was reduced to 1.50 mg every 6 hours for he second week, 0.75 mg every 6 hours in the third week, and 0.375 mg every 6 hours in the fourth week

paediatric dosage was derived from a standard table based on surface area

	Antituberculosis chemotherapy: isoniazid (10 mg/kg of body weight/day, or 20 mg/kg of body weight/day in children less than 2 years of age) and streptomycin (20 mg/kg of body weight/day, up to a maximum of 1 g); total duration of antituberculosis chemotherapy unclear All patients received high doses of vitamin B_6
Comparison	*Antituberculosis chemotherapy plus placebo* Placebo (4 weeks) adults received 2.25 mg parenterally every 6 hours during the first week; the dose was reduced to 1.50 mg every 6 hours for he second week, 0.75 mg every 6 hours in the third week, and 0.375 mg every 6 hours in the fourth week paediatric dosage was derived from a standard table based on surface area Antituberculosis chemotherapy: isoniazid (10 mg/kg of body weight/day, or 20 mg/kg of body weight/day in children less than 2 years of age) and streptomycin (20 mg/kg of body weight/day, up to a maximum of 1 g); total duration of antituberculosis chemotherapy unclear All patients received high doses of vitamin B_6
Length of follow up	Unclear
Location	Calcutta, India
Outcomes measures and effect size	**Mortality** Number of deaths dexamethasone group = 6 of 11 placebo group = 9 of 12 OR[1] (95% CI) = 0.40 (0.07 to 2.34) i.e. not statistically significant Number of deaths amongst those <2 years of age dexamethasone group = 2 of 2

	placebo group = 3 of 3 OR[1] (95% CI) = 0.71 (0.01 to 49.71) i.e. not statistically significant Number of deaths amongst those classed as stage 2 on admission dexamethasone group = 3 of 6 placebo group = 5 of 8 OR[1] (95% CI) = 0.60 (0.07 to 5.14) i.e. not statistically significant Number of deaths amongst those classed as stage 3 on admission dexamethasone group = 3 of 4 placebo group = 4 of 4 OR[1] (95% CI) = 0.26 (0.01 to 8.52) i.e. not statistically significant (Mean) survival time (days) dexamethasone group = 14 placebo group = 14 MD[2] = 0
Source of funding	No details provided
Comments	

[1] Odds ratio and 95% confidence interval calculated by reviewer

[2] Mean difference calculated by reviewer

Abbreviations: CI, confidence intervals; CSF, cerebrospinal fluid; MD, mean difference; OR, odds ratio; RCT, randomised controlled trial

1.1.16 Kumarvelu et al, 1994

Bibliographic reference	Kumarvelu S, Prasad K, Khosla A et al (1994) Randomised controlled trial of dexamethasone in tuberculous meningitis. Tubercle and Lung Disease 75(3): 203-7
Study type	RCT
Study quality	*Appropriate method of randomisation used?* yes – random numbers table *Allocation concealment used?* unclear *Blinding used?* unclear *Groups comparable at baseline?* yes *Groups received the same care apart from the intervention(s) studied?* yes *Groups followed up for an equal and appropriate length of time?* follow-up was equal in both groups although was only for 3 months after treatment initiation (i.e. not for the full treatment period) *Groups comparable for treatment completion and availability of outcome data?* yes *Study used precise definitions and reliable measures of outcome?*

	‘full/partial recovery’ and ‘unchanged’ status not defined *Population studied is the same as the population of interest?* yes *Intervention used is the same as the intervention of interest?* antituberculosis chemotherapeutic regimens lacked ethambutol *Have substitute outcomes been used instead of the patient-important outcomes of interest?* yes – used composites of outcomes of interest: ‘poor’ and ‘good’ outcome were composites of mortality and changes in signs and symptoms *Analysis followed the intent-to-treat principle?* some data was only available for patients with either ‘severe’ or ‘mild-to-moderate’ disease on admission who survived; since the authors do not provide the number of patients with either ‘severe’ or ‘mild-to-moderate’ disease on admission who were randomised to each intervention, this data could not be analysed in accordance with the intent-to-treat principle
Number of patients	Randomised = 47 dexamethasone group = 24 antituberculosis chemotherapy alone group = 23 Outcome data available at 3 months = 41 dexamethasone group = 20 antituberculosis chemotherapy alone group = 21
Patient characteristics	*Inclusion* Probable tuberculous meningitis *Diagnostic criteria* Diagnosis of probable tuberculous meningitis was made if at least 3 of the following criteria were present:

clinical: fever >38°C, headache, neck stiffness with or without seizures or altered sensorium for at least 2 weeks

characteristic CSF findings: leukocytes >20 /mm^3 with lymphocytotic predominance, proteins >1 g/l, sugar <2/3 of corresponding blood sugar, cultures negative for pyrogenic organisms and fungi, and negative cytology for malignant cells

contrast-enhanced CT scan of the head: basal exudates or hydrocephalus with or without infarcts and tuberculoma

clinical, radiological or histological evidence of extracranial tuberculosis

Severity of disease

Analysed on admission using the following scoring system:

Parameter	**Weightage (points)**
Sensorium	
normal	1
delirium	2
drowsy	3
semi-coma	4
coma	5
Associated pulmonary tuberculosis	0.5
Associated extensive tuberculous or non-tuberculous disease	0.5
Age <10 years or >50 years	0.5
CSF protein >3 g/l	0.5
CT scan evidence	
exudates	

grade I	1
grade II	2
grade III	3
hydrocephalus	
mild	1
moderate	2
severe	3
mid-line shift	1
Leukopenia or leukocytosis	0.5
Systolic hypotension	1

'Severe' disease = a score of 8 or more

'Mild-to-moderate' disease = a score of less than 8

Exclusion

Aged <10 years

Previous antituberculosis chemotherapy for >4 weeks

Previous glucocorticoid use

Baseline

	Dexamethasone group	**Antituberculosis chemotherapy alone**
Clinical features		
hypotension, %	29	13

		meningeal signs, %	92	100	
		altered sensorium, %	92	74	
		seizures, %	46	30	
		papilloedema, %	50	22	
		cerebrovascular event, %	29	35	
		spinal arachnoiditis, %	17	4	
		extrameningeal tuberculosis, %	46	52	
		CSF parameters			
		abnormal cell count, %	83	100	
		lymphocyte predominance, %	63	61	
		raised proteins, %	75	83	
		low glucose levels, %	91	88	
		CT parameters			
		exudates, %	79	91	
		hydrocephalus, %	58	52	
		infarct, %	13	22	
		tuberculoma, %	21	9	
Intervention	*Antituberculosis chemotherapy plus dexamethasone* Dexamethasone (6 weeks) adults: 16 mg divided into 4 doses in the first week, followed by 8 mg/day for 21 days, after which doses were tapered				

	off over the next 14 days children: 0.6 mg/kg of body weight/day for the first 7 days, followed by 0.3 mg/kg of body weight/day for 21 days, after which doses were tapered off over the next 14 days Antituberculosis chemotherapy: isoniazid (300 mg/day in adults, or 10 mg/kg of body weight/day in children), rifampicin (450 mg/day in adults, or 15 mg/kg of body weight/day in children) and pyrazinamide (1500 mg/day in adults, or 30 mg/kg of body weight/day in children); total duration of antituberculosis chemotherapy unknown Pyridoxine supplements were given routinely
Comparison	*Antituberculosis chemotherapy alone* Antituberculosis chemotherapy: isoniazid (300 mg/day in adults, or 10 mg/kg of body weight/day in children), rifampicin (450 mg/day in adults, or 15 mg/kg of body weight/day in children) and pyrazinamide (1500 mg/day in adults, or 30 mg/kg of body weight/day in children); total duration of antituberculosis chemotherapy unknown Pyridoxine supplements were given routinely
Length of follow up	3 months after treatment initiation
Location	New Delhi, India
Outcomes measures and effect size	**Mortality** Number of deaths dexamethasone group = 9 of 24 antituberculosis chemotherapy alone group = 9 of 23 OR[1] (95% CI) = 0.93 (0.29 to 3.03) i.e. not statistically significant
	Response to treatment – full/partial recovery Definition not provided Number of patients to achieve a full or partial recovery

	dexamethasone group = 15 of 24 antituberculosis chemotherapy alone group = 13 of 23 OR[1] (95% CI) = 1.28 (0.40 to 4.12) i.e. not statistically significant Number of patients who were defined as 'severe' on admission and to survive to achieve a full or partial recovery dexamethasone group = 4 of 4 antituberculosis chemotherapy alone group = 1 of 2 OR[1] (95% CI) = 9.00 (0.22 to 362.50) i.e. not statistically significant Number of patients who were defined as 'mild-to-moderate' on admission and to survive to achieve a full or partial recovery dexamethasone group = 11 of 11 antituberculosis chemotherapy alone group = 12 of 12 OR[1] (95% CI) = 0.92 (0.02 to 50.28) i.e. not statistically significant
	Response to treatment – unchanged status Definition not provided Number of patients whose status was unchanged dexamethasone group = 0 of 24 antituberculosis chemotherapy alone group = 1 of 23 OR[1] (95% CI) = 0.31 (0.01 to 7.91)

	i.e. not statistically significant Number of patients who were defined as 'severe' on admission and to survive whose status was unchanged dexamethasone group = 0 of 4 antituberculosis chemotherapy alone group = 1 of 2 OR[1] (95% CI) = 0.11 (0.00 to 4.48) i.e. not statistically significant Number of patients who were defined as 'mild-to-moderate' on admission and to survive whose status was unchanged dexamethasone group = 0 of 11 antituberculosis chemotherapy alone group = 0 of 12 OR[1] (95% CI) = 1.09 (0.02 to 59.40) i.e. not statistically significant
	Response to treatment – 'poor' outcome Defined as death or survival with major sequelae (persistent vegetative state, blindness, symptomatic hydrocephalus, moderate-to-severe intellectual impairment, severe functional disability (totally dependent), or uncontrolled seizures) Number of patients to experience a poor outcome dexamethasone group = 5 of 24 antituberculosis chemotherapy alone group = 8 of 23 OR[1] (95% CI) = 0.49 (0.13 to 1.82) i.e. not statistically significant
	Response to treatment – 'good' outcome Defined as survival with minor (mild intellectual impairment, mild-to-moderate functional disability (able to enact the activities of daily living with minimal or no assistance)) or no sequelae

	Number of patients to experience a good outcome dexamethasone group = 15 of 24 antituberculosis chemotherapy alone group = 13 of 23 OR[1] (95% CI) = 1.28 (0.40 to 4.12) i.e. not statistically significant
	Changes in signs and symptoms – sensorium Time (mean, days) to recovery of sensorium amongst patients who survived dexamethasone group (n = 15)[2] = 14.6 antituberculosis chemotherapy alone group (n = 14)[2] = 11.3 MD[3] = 3.3 Time (mean, days) to recovery of sensorium amongst patients who were defined as 'severe' on admission and who survived dexamethasone group (n = 4) = 19 antituberculosis chemotherapy alone group (n = 2) = 25 MD[3] = -6 Time (mean, days) to recovery of sensorium amongst patients who were defined as 'mild-to-moderate' on admission and who survived dexamethasone group (n = 11) = 13 antituberculosis chemotherapy alone group (n = 12) = 9 MD[3] = 4
	Changes in signs and symptoms – fever Time (mean, days) to recovery of fever amongst patients who survived

	dexamethasone group (n = 15)[2] = 13 antituberculosis chemotherapy alone group (n = 14)[2] = 10.3 MD[3] = 2.7 Time (mean, days) to recovery of fever amongst patients who were defined as 'severe' on admission and who survived dexamethasone group (n = 4) = 13 antituberculosis chemotherapy alone group (n = 2) = 18 MD[3] = -5 Time (mean, days) to recovery of fever amongst patients who were defined as 'mild-to-moderate' on admission and who survived dexamethasone group (n = 11) = 13 antituberculosis chemotherapy alone group (n = 12) = 9 MD[3] = 4
	Changes in signs and symptoms – headache Time (mean, days) to recovery of headache amongst patients who survived dexamethasone group (n = 15)[2] = 18.5 antituberculosis chemotherapy alone group (n = 14)[2] = 11.1 MD[3] = 7.4 Time (mean, days) to recovery of headache amongst patients who were defined as 'severe' on admission and who survived dexamethasone group (n = 4) = 20 antituberculosis chemotherapy alone group (n = 2) = 12 MD[3] = 8

	Time (mean, days) to recovery of headache amongst patients who were defined as 'mild-to-moderate' on admission and who survived dexamethasone group (n = 11) = 18 antituberculosis chemotherapy alone group (n = 12) = 11 MD[3] = 7
	Changes in signs and symptoms – cognitive status Assessed using a mini-mental score (tests orientation, registration, calculation, recall and language functions; scores range from 0 to 30, with 0 being the worst performance and 30 being 'normal') Time (mean, days) to improvement in mini-mental score amongst patients who survived dexamethasone group (n = 15)[2] = 8.3 antituberculosis chemotherapy alone group (n = 14)[2] = 4.9 MD[3] = 3.4 Time (mean, days) to improvement in mini-mental score amongst patients who were defined as 'severe' on admission and who survived dexamethasone group (n = 4) = 9 antituberculosis chemotherapy alone group (n = 2) = 10 MD[3] = -1 Time (mean, days) to improvement in mini-mental score amongst patients who were defined as 'mild-to-moderate' on admission and who survived dexamethasone group (n = 11) = 8 antituberculosis chemotherapy alone group (n = 12) = 4 MD[3] = 4
	Changes in signs and symptoms – activity of daily living

	Assessed using the Barthel index (includes bowel and bladder control, grooming, toilet use, feeding, transfer, mobility, dressing, walking upstairs and bathing; a score of 0 indicates a totally dependent patient, whereas a score of 20 means an independent existence) Time (mean, days) to improvement in Barthel score amongst patients who survived dexamethasone group (n = 15)[2] = 7.6 antituberculosis chemotherapy alone group (n = 14)[2] = 2.3 MD[3] = 5.3 Time (mean, days) to improvement in Barthel score amongst patients who were defined as 'severe' on admission and who survived dexamethasone group (n = 4) = 12 antituberculosis chemotherapy alone group (n = 2) = 4 MD[3] = 8 Time (mean, days) to improvement in Barthel score amongst patients who were defined as 'mild-to-moderate' on admission and who survived dexamethasone group (n = 11) = 6 antituberculosis chemotherapy alone group (n = 12) = 2 MD[3] = 4
Source of funding	No details provided
Comments	

[1] Odds ratio and 95% confidence interval calculated by reviewer

[2] Data for those with severe disease on admission who survived and those with mild-to-moderate disease on admission who survived was combined into a pooled mean difference by reviewer

[3] Mean difference calculated by reviewer

Abbreviations: CI, confidence intervals; CSF, cerebrospinal fluid; CT, computerised tomography; H, isoniazid; OR, odds ratio; R, rifampicin; RCT, randomised controlled trial; S, streptomycin; TB, tuberculosis

1.1.17 Schoeman et al, 1997

Bibliographic reference	Schoeman JF, Van Zyl LE, Laubscher JA et al (1997) Effect of corticosteroids on intracranial pressure, computed tomographic findings, and clinical outcome in young children with tuberculous meningitis. Pediatrics 99(2): 226-31
Study type	RCT
Study quality	*Appropriate method of randomisation used?* unclear *Allocation concealment used?* unclear *Blinding used?* blinded: clinical psychologist assessing intelligence, clinician testing hearing, ophthalmologist testing vision, and physical therapist testing motor function unclear patients or other health professionals were blinded *Groups comparable at baseline?* yes, although details provided are limited *Groups received the same care apart from the intervention(s) studied?* yes *Groups followed up for an equal and appropriate length of time?* yes *Groups comparable for treatment completion and availability of outcome data?* yes

	Study used precise definitions and reliable measures of outcome? yes *Population studied is the same as the population of interest?* yes *Intervention used is the same as the intervention of interest?* yes *Have substitute outcomes been used instead of the patient-important outcomes of interest?* yes *Analysis followed the intent-to-treat principle?* yes
Number of patients	Randomised = 141 prednisolone group = 70 antituberculosis chemotherapy alone group = 71 Outcome data available for incidence of mortality and the incidence of tuberculoma = 141 prednisolone group = 70 antituberculosis chemotherapy alone group = 71 Outcome data available for IQ = 119 prednisolone group = 65 antituberculosis chemotherapy alone group = 54 Outcome data available for motor function = 126 prednisolone group = 66

	antituberculosis chemotherapy alone group = 60 Outcome data available for vision = 119 prednisolone group = 63 antituberculosis chemotherapy alone group = 56 Outcome data available for hearing = 116 prednisolone group = 60 antituberculosis chemotherapy alone group = 56
Patient characteristics	*Inclusion* Tuberculous meningitis Children (age threshold not provided) *Diagnostic criteria* Based on history and typical CSF changes, together with 2 or more of the following: strongly positive (>15 mm) Mantoux test chest radiograph findings suggesting tuberculosis i.e. a miliary picture or hilar lymph node adenopathy, often accompanied by a segmental lesion acute hydrocephalus with basal enhancement on CT scanning isolation of *M. tuberculosis* in gastric aspirate and/or CSF *Severity of disease* Classified according to the system of the British Medical Research Council: stage 1: mild cases; without altered consciousness or focal neurologic signs stage 2: moderately advanced cases; altered consciousness; not comatose; moderate neurologic deficits, such as single cranial nerve palsies, parapesis and hemiparesis

<table>
<tr><td></td><td>
stage 3: severe cases; comatose patients; multiple cranial nerve palsies; hemiplegia and/or paraplegia

Only patients with stage 2 or 3 were included

Baseline
<table>
<tr><th></th><th>Prednisolone group</th><th>Placebo group</th></tr>
<tr><td>Severity of disease
stage 2, n
stage 3, n</td><td>
37
33</td><td>
36
35</td></tr>
<tr><td>Baseline pressure (mean±SD), mm Hg</td><td>28.5±12.7</td><td>26.0±11.8</td></tr>
<tr><td>Pulse pressure (mean±SD), mm Hg</td><td>6.1±5.5</td><td>5.6±5.8</td></tr>
<tr><td>Ventricular size (mean±SD), ratio of biventricular diameter to biparietal diameter</td><td>0.26±0.08</td><td>0.25±0.08</td></tr>
</table>
</td></tr>
<tr><td>Intervention</td><td>
Antituberculosis chemotherapy plus prednisolone

Prednisolone (1 month)

2 to 4 mg/kg of body weight/day - the first 16 patients in the steroid group received prednisolone at 2 mg/kg/day, and the remaining patients received 4 mg/kg/day[2]

Antituberculosis chemotherapy: 6HRZE

20 mg/kg of body weight/day isoniazid, 20 mg/kg of body weight/day rifampicin, 40 mg/kg of body weight/day pyrazinamide and 20 mg/kg of body weight/day ethambutol daily for 6 months

All children with communicating hydrocephalus were treated with daily acetazolamide (100 mg/kg of bodyweight) and furosemide (1 mg/kg of bodyweight) for 1 month

All children with non-communicating hydrocephalus were referred for immediate ventriculoperitoneal shunting surgery
</td></tr>
</table>

Comparison	*Antituberculosis chemotherapy alone* Antituberculosis chemotherapy: 6HRZE 20 mg/kg of body weight/day isoniazid, 20 mg/kg of body weight/day rifampicin, 40 mg/kg of body weight/day pyrazinamide and 20 mg/kg of body weight/day ethambutol daily for 6 months All children with communicating hydrocephalus were treated with daily acetazolamide (100 mg/kg of bodyweight) and furosemide (1 mg/kg of bodyweight) for 1 month All children with non-communicating hydrocephalus were referred for immediate ventriculoperitoneal shunting surgery
Length of follow up	6 months from treatment initiation (i.e. full treatment period)
Location	South Africa
Outcomes measures and effect size	**Mortality** Number of deaths prednisolone group = 4 of 70 antituberculosis chemotherapy alone group = 13 of 71 **OR[1] (95% CI) = 0.28 (0.09 to 0.90)** **i.e. statistically significant** Number of deaths among those classified as stage 2 on admission prednisolone group = 1 of 37 antituberculosis chemotherapy alone group = 1 of 36 OR[1] (95% CI) = 0.97 (0.06 to 16.16) i.e. not statistically significant Number of deaths among those classified as stage 3 on admission prednisolone group = 3 of 33

	antituberculosis chemotherapy alone group = 12 of 35 **OR[1] (95% CI) = 0.19 (0.05 to 0.76)** **i.e. statistically significant**
	Changes in signs and symptoms - disability Number of patients to be disabled (severely or mildly) at 6 months prednisolone group = 54 of 70 antituberculosis chemotherapy alone group = 49 of 71 OR[1] (95% CI) = 1.52 (0.71 to 3.21) i.e. not statistically significant Number of patients to be severely disabled at 6 months prednisolone group = 14 of 70 antituberculosis chemotherapy alone group = 19 of 71 OR[1] (95% CI) = 0.68 (0.31 to 1.50) i.e. not statistically significant
	Changes in signs and symptoms - tuberculoma Number of patients to develop tuberculomas in the first month of treatment prednisolone group = 2 of 70 antituberculosis chemotherapy alone group = 9 of 71 **OR[1] (95% CI) = 0.20 (0.04 to 0.97)** **i.e. statistically significant**
	Changes in signs and symptoms - IQ

	Number of patients to have an IQ of less than 75 at 6 months prednisolone group = 31 of 70 antituberculosis chemotherapy alone group = 36 of 71 OR[1] (95% CI) = 0.77 (0.40 to 1.50) i.e. not statistically significant
	Changes in signs and symptoms – motor function Number of patients to be experience hemiplegia or quadriplegia at 6 months prednisolone group = 24 of 70 antituberculosis chemotherapy alone group = 24 of 71 OR[1] (95% CI) = 1.02 (0.51 to 2.05) i.e. not statistically significant
	Changes in signs and symptoms - vision Number of patients with visual deterioration (decreased vision or blindness) at 6 months prednisolone group = 9 of 70 antituberculosis chemotherapy alone group = 7 of 71 OR[1] (95% CI) = 1.35 (0.47 to 3.85) i.e. not statistically significant Number of patients to be blind at 6 months prednisolone group = 3 of 70 antituberculosis chemotherapy alone group = 3 of 71 OR[1] (95% CI) = 1.01 (0.20 to 5.21)

	i.e. not statistically significant
	Changes in signs and symptoms - hearing Number of patients with deterioration in their hearing (decreased hearing, though not deaf) at 6 months prednisolone group = 3 of 70 antituberculosis chemotherapy alone group = 6 of 71 OR[1] (95% CI) = 0.49 (0.12 to 2.02) i.e. not statistically significant Number of patients to be deaf at 6 months prednisolone group = 0 of 70 antituberculosis chemotherapy alone group = 0 of 71 OR[1] (95% CI) = 1.01 (0.02 to 51.82) i.e. not statistically significant
Source of funding	South Africa Medical Research Council
Comments	

[1] Odds ratio and 95% confidence interval calculated by reviewer

[2] The doubling of the dose was enacted when the investigators became aware of a study that showed rifampicin to decrease the bioavailability of prednisolone by 66% and increased the plasma clearance of the drug by 45%

Abbreviations: CI, confidence intervals; CSF, cerebrospinal fluid; CT, computed tomography; H, isoniazid; OR, odds ratio; R, rifampicin; RCT, randomised controlled trial; S, streptomycin; TB, tuberculosis

1.1.18 Thwaites et al, 2004/7 / Török et al, 2011

Study type	RCT

Study quality	*Appropriate method of randomisation used?* yes – computer-generated sequence of random numbers was used to allocate treatment in blocks of 30 *Allocation concealment used?* yes *Blinding used?* double-blinded: placebo and dexamethasone were identical in appearance; all participants, enrolling physicians, and investigators remained blinded to the treatment allocation until the last patient completed follow-up *Groups comparable at baseline?* yes *Groups received the same care apart from the intervention(s) studied?* yes *Groups followed up for an equal and appropriate length of time?* yes *Groups comparable for treatment completion and availability of outcome data?* yes *Study used precise definitions and reliable measures of outcome?* yes *Population studied is the same as the population of interest?* yes *Intervention used is the same as the intervention of interest?* yes

	Have substitute outcomes been used instead of the patient-important outcomes of interest? no *Analysis followed the intent-to-treat principle?* yes
Number of patients	Randomised = 545 dexamethasone group = 274 placebo group = 271 Lost to follow-up (last observation carried forward) = 62 dexamethasone group = 35 placebo group = 27
Patient characteristics	*Inclusion* Clinical evidence of meningitis Over 14 years of age *Diagnostic criteria* Combination of nuchal rigidity and CSF abnormalities 'Definite' tuberculosis = acid-fast bacilli were seen in the CSF 'Probable tuberculosis = patients with one or more of the following: suspected active pulmonary tuberculosis on chest radiography acid-fast bacilli found in any specimen other than the CSF clinical evidence of other extrapulmonary tuberculosis 'Possible" tuberculosis = patients with at least four of the following:

a history of tuberculosis, predominance of lymphocytes in the CSF

a duration of illness of more than five days

a ratio of CSF glucose to plasma glucose of less than 0.5

altered consciousness

yellow cerebrospinal fluid

focal neurologic signs

Severity of disease

Patients were stratified on entry according to the British Medical Research Council criteria, modified as follows:

stage 1 = a score on the Glasgow coma scale of 15 (possible range, 3 to 15, with higher scores indicating better status) with no focal neurologic signs

stage 2 = a score on the Glasgow coma scale of either 11 to 14, or of 15 with focal neurologic signs

stage 3 = a score on the Glasgow coma score of 10 or less

Exclusion

Corticosteroids contraindicated

>1 dose of any corticosteroid

>30 days of antituberculosis chemotherapy immediately before study entry

Baseline

	Dexamethasone (n = 274)	**Placebo** (n = 271)
Age		
median, years	36.0	35.0

		range, years	15–88	15–84	
		Sex			
		male, n (%)	168 (61.3)	163 (60.1)	
		Diagnosis			
		definite	98 (35.8)	89 (32.8)	
		probable	130 (47.4)	131 (48.3)	
		possible	44 (16.1)	47 (17.3)	
		not tuberculous meningitis	2 (0.7)	4 (1.5)	
		Weight			
		median, kg	45.0	45.0	
		range, kg	25–75	30–70	
		Score on the Glasgow coma scale			
		median	14	14	
		range	3–15	3–15	
		Cranial nerve palsy, n (%)	82 (29.9)	74 (27.3)	
		Hemiparesis, n (%)	48 (17.5)	37 (13.7)	
		Paraparesis, n (%)	28 (10.2)	11 (4.1)	
		Severity of disease			
		stage 1, n (%)	90 (32.8)	86 (31.7)	
		stage 2, n (%)	122 (44.5)	125 (46.1)	
		stage 3, n (%)	62 (22.6)	60 (22.1)	

<table>
<tr><td></td><td>
<table>
<tr><td>HIV status</td><td></td><td></td></tr>
<tr><td>positive, n (%)</td><td>44 (16.1)</td><td>54 (19.9)</td></tr>
<tr><td>negative, n (%)</td><td>227 (82.8)</td><td>209 (77.1)</td></tr>
<tr><td>Lymphocyte count</td><td></td><td></td></tr>
<tr><td>CD4</td><td></td><td></td></tr>
<tr><td>median, /mm3</td><td>64</td><td>66</td></tr>
<tr><td>range, /mm3</td><td>14–694</td><td>7–359</td></tr>
<tr><td>CD8</td><td></td><td></td></tr>
<tr><td>median, /mm3</td><td>606</td><td>386</td></tr>
<tr><td>range, /mm3</td><td>134–998</td><td>28–1001</td></tr>
</table>
</td></tr>
<tr><td>Intervention</td><td>Antituberculosis chemotherapy plus dexamethasone

Dexamethasone sodium phosphate (8 weeks)

stage 1 disease: received 2 weeks of intravenous therapy (0.3 mg/kg of body weight/day for week 1 and 0.2 mg/kg of body weight/day for week 2) and then 4 weeks of oral therapy (0.1 mg/kg of body weight/day for week 3, then a total of 3 mg/day, decreasing by 1 mg each week)

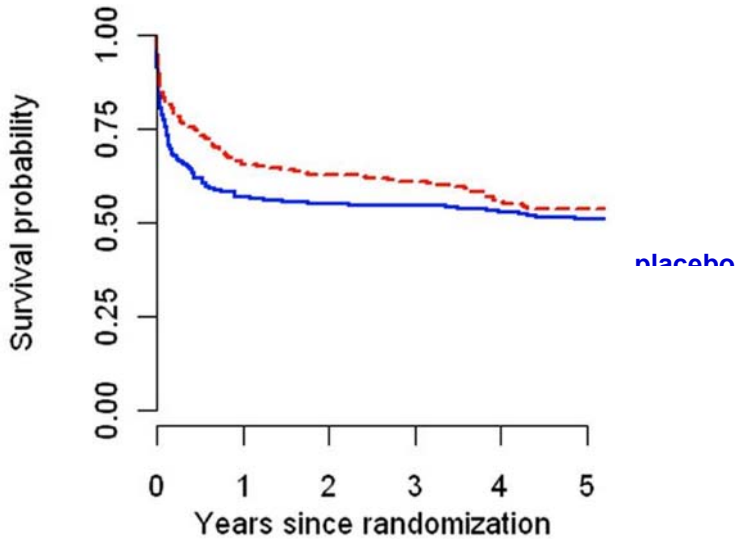
stage 2 or 3 disease: received intravenous treatment for 4 weeks (0.4 mg/kg of body weight/day for week 1, 0.3 /kg of body weight/day for week 2, 0.2 /kg of body weight/day for week 3, and 0.1 /kg of body weight/day for week 4) and then oral treatment for 4 weeks, starting at a total of 4 mg/day and decreasing by 1 mg each week

Antituberculosis chemotherapy:

3HRZS/6HRZ – 5 mg/kg of body weight/day isoniazid, 10 mg/kg of body weight/day rifampicin, 25 mg/kg of body weight/day pyrazinamide and 20 mg/kg of body weight/day streptomycin (up to a maximum of 1 g/day) daily for 3 months, followed by isoniazid, rifampicin and pyrazinamide for 6 months</td></tr>
</table>

	HIV-positive patients: 3HRZE/6HRZ – 5 mg/kg of body weight/day isoniazid, 10 mg/kg of body weight/day rifampicin, 25 mg/kg of body weight/day pyrazinamide and 20 mg/kg of body weight/day ethambutol (up to a maximum of 1.2 g/day) daily for 3 months, followed by isoniazid, rifampicin and pyrazinamide for 6 months previously treated patients: 3HRZSE/6HRZ – 5 mg/kg of body weight/day isoniazid, 10 mg/kg of body weight/day rifampicin, 25 mg/kg of body weight/day pyrazinamide, 20 mg/kg of body weight/day streptomycin (up to a maximum of 1 g/day) and 20 mg/kg of body weight/day ethambutol (up to a maximum of 1.2 g/day) daily for 3 months, followed by isoniazid, rifampicin and pyrazinamide for 6 months None of the patients received antiretroviral drugs
Comparison	*Antituberculosis chemotherapy plus placebo* Placebo (8 weeks) stage 1 disease: received 2 weeks of intravenous therapy (0.3 mg/kg of body weight/day for week 1 and 0.2 mg/kg of body weight/day for week 2) and then 4 weeks of oral therapy (0.1 mg/kg of body weight/day for week 3, then a total of 3 mg/day, decreasing by 1 mg each week) stage 2 or 3 disease: received intravenous treatment for 4 weeks (0.4 mg/kg of body weight/day for week 1, 0.3 /kg of body weight/day for week 2, 0.2 /kg of body weight/day for week 3, and 0.1 /kg of body weight/day for week 4) and then oral treatment for 4 weeks, starting at a total of 4 mg/day and decreasing by 1 mg each week Antituberculosis chemotherapy: 3HRZS/6HRZ – 5 mg/kg of body weight/day isoniazid, 10 mg/kg of body weight/day rifampicin, 25 mg/kg of body weight/day pyrazinamide and 20 mg/kg of body weight/day streptomycin (up to a maximum of 1 g/day) daily for 3 months, followed by isoniazid, rifampicin and pyrazinamide for 6 months HIV-positive patients: 3HRZE/6HRZ – 5 mg/kg of body weight/day isoniazid, 10 mg/kg of body weight/day rifampicin, 25 mg/kg of body weight/day pyrazinamide and 20 mg/kg of body weight/day ethambutol (up to a maximum of 1.2 g/day) daily for 3 months, followed by isoniazid, rifampicin and pyrazinamide for 6 months previously treated patients: 3HRZSE/6HRZ – 5 mg/kg of body weight/day isoniazid, 10 mg/kg of body weight/day rifampicin, 25 mg/kg of body weight/day pyrazinamide, 20 mg/kg of body weight/day streptomycin (up to a maximum of 1 g/day) and 20 mg/kg of body weight/day ethambutol (up to a maximum of 1.2 g/day) daily for 3 months, followed by isoniazid, rifampicin and pyrazinamide for 6 months None of the patients received antiretroviral drugs

Location	Ho Chi Minh City, Vietnam
Bibliographic reference	Török ME, Bang ND, Chau TTH et al (2011) Dexamethasone and Long-Term Outcome of Tuberculous Meningitis in Vietnamese Adults and Adolescents. PLoS One 6(12): e27821
Length of follow up	5 years after randomisation
Outcomes measures and effect size	**Mortality** **Years after treatment initiation** / **Dexamethasone** (n = 274) / **Placebo** (n = 271) / **Difference in survival rate (95% CI); p-value** Number at risk / Survival rate (95% CI) / Number at risk / Survival rate (95% CI) **0**: 274 / - / 271 / - / - **1**: 160 / 0.65 (0.60 to 0.71) / 131 / 0.57 (0.51 to 0.63) / 0.09 (0.00 to 0.17); p = 0.04 **2**: 152 / 0.63 (0.57 to 0.69) / 125 / 0.55 (0.49 to 0.69) / 0.08 (0.00 to 0.16); p = 0.07 **3**: 147 / 0.61 (0.55 to 0.67) / 124 / 0.55 (0.49 to 0.61) / 0.06 (-0.02 to 0.15); p = 0.15 **4**: 130 / 0.55 (0.50 to 0.62) / 117 / 0.53 (0.47 to 0.59) / 0.03 (-0.06 to 0.11); p = 0.56 **5**: 82 / 0.54 (0.48 to 0.60) / 64 / 0.51 (0.45 to 0.57) / 0.03 (-0.06 to 0.12); p = 0.51



Hazard ratio 0 to 3 months after randomisation (not intent-to-treat):

HR (95% CI) = 0.62 (0.44 to 0.88)

p = 0.01

i.e. statistically significant

Hazard ratio more than 3 months after randomisation (not intent-to-treat):

HR (95% CI) = 1.50 (1.00 to 2.26)

p = 0.05

i.e. statistically significant

Number of deaths 5 years after randomisation:

dexamethasone group = 121 of 274

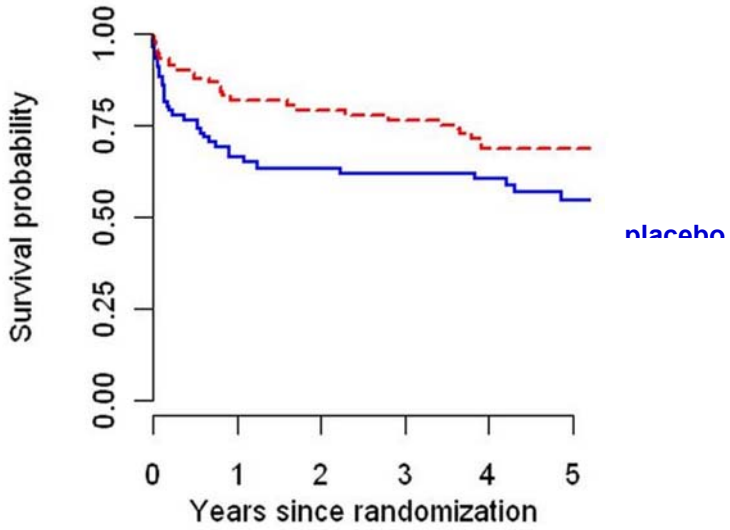
placebo group = 128 of 271

OR[1] (95% CI) = 0.88 (0.63 to 1.24)

i.e. not statistically significant

Stage 1 disease:

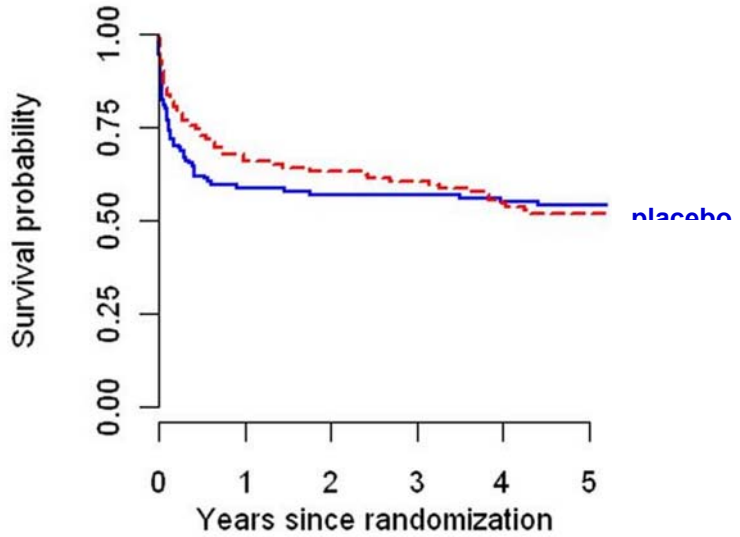
Years after treatment initiation	**Dexamethasone** (n = 90)		**Placebo** (n = 86)		**Difference in survival rate (95% CI); p-value**
	Number at risk	Survival rate (95% CI)	Number at risk	Survival rate (95% CI)	
0	90	-	86	-	-
1	65	0.82 (0.74 to 0.90)	46	0.66 (0.57 to 0.77)	0.15 (0.02 to 0.29); p = 0.02
2	61	0.79 (0.71 to 0.88)	42	0.63 (0.54 to 0.75)	0.16 (0.02 to 0.29); p = 0.02
3	59	0.71 (0.68 to 0.86)	41	0.62 (0.52 to 0.74)	0.15 (0.01 to 0.29); p = 0.04
4	53	0.69 (0.59 to 0.80)	39	0.60 (0.50 to 0.72)	0.08 (-0.06 to 0.23); p = 0.27
5	34	0.69 (0.59 to 0.80)	23	0.55 (0.44 to 0.68)	0.14 (-0.01 to 0.29); p = 0.07



Stage 2 disease:

Years after treatment initiation	Dexamethasone (n = 122)		Placebo (n = 125)		Difference in survival rate (95% CI); p-value
	Number at risk	Survival rate (95% CI)	Number at risk	Survival rate (95% CI)	
0	122	-	125	-	-
1	72	0.66 (0.58 to 0.75)	65	0.59 (0.51 to 0.68)	0.07 (-0.05 to 0.19); p = 0.25
2	69	0.63 (0.55 to 0.72)	63	0.57 (0.49 to 0.66)	0.06 (-0.06 to 0.19); p = 0.33
3	66	0.60 (0.52 to 0.70)	63	0.57 (0.49 to 0.66)	0.03 (-0.09 to 0.16); p = 0.59
4	57	0.55 (0.46 to	60	0.55 (0.47 to	0.00 (-0.18 to 0.17); p =

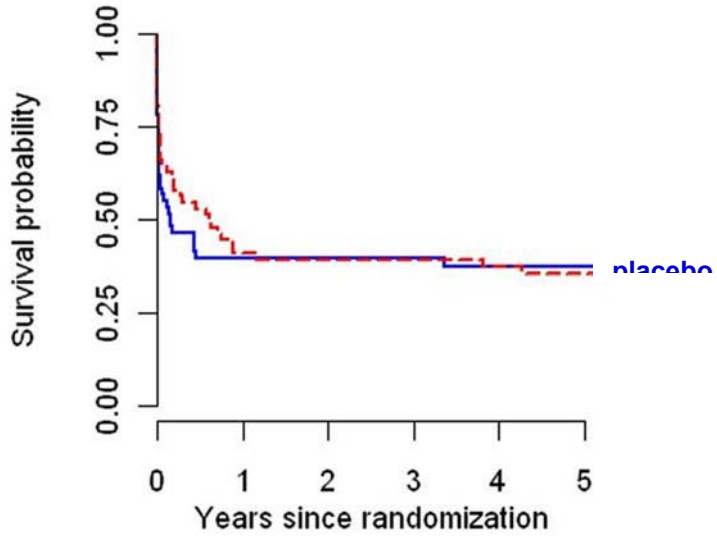
		0.65)		0.65)	0.98
5	34	0.52 (0.43 to 0.62)	33	0.54 (0.46 to 0.64)	-0.02 (-0.15 to 0.11); p = 0.73



Stage 3 disease:

Years after treatment initiation	**Dexamethasone** (n = 62)		**Placebo** (n = 60)		**Difference in survival rate (95% CI); p-value**
	Number at risk	Survival rate (95% CI)	Number at risk	Survival rate (95% CI)	
0	62	-	60	-	-
1	23	0.41 (0.30 to 0.55)	20	0.39 (0.29 to 0.54)	0.01 (-0.16 to 0.19); p = 0.88
2	22	0.39 (0.28 to 0.54)	20	0.39 (0.29 to 0.54)	0.00 (-0.18 to 0.17); p = 0.96

3	22	0.39 (0.28 to 0.54)	20	0.39 (0.29 to 0.54)	0.00 (-0.18 to 0.17); p = 0.96
4	20	0.37 (0.27 to 0.52)	18	0.38 (0.27 to 0.52)	0.00 (-0.18 to 0.17); p = 0.98
5	14	0.35 (0.25 to 0.50)	8	0.38 (0.27 to 0.52)	-0.02 (-0.20 to 0.15); p = 0.81



Changes in signs and symptoms – disability

Number of patients in a good disability status 5 years after randomisation:

dexamethasone group = 69 of 274

placebo group = 61 of 271

OR[1] (95% CI) = 1.14 (0.77 to 1.69)

i.e. not statistically significant

	Number of patients in an intermediate disability status 5 years after randomisation: dexamethasone group = 43 of 274 placebo group = 36 of 271 OR[1] (95% CI) = 1.22 (0.75 to 1.96) i.e. not statistically significant Number of patients in a severe disability status 5 years after randomisation: dexamethasone group = 17 of 274 placebo group = 18 of 271 OR[1] (95% CI) = 0.93 (0.47 to 1.84) i.e. not statistically significant
Bibliographic reference	Thwaites GE, Bang ND, Dung NH et al (2004) Dexamethasone for the treatment of tuberculous meningitis in adolescents and adults. New England Journal of Medicine 351: 1741-51
Length of follow up	9 months after treatment initiation
Outcomes measures and effect size	**Changes in signs and symptoms – fever** Time to fever clearance (median, days from randomisation to observation of a maximal daily temperature of less than 37.5°C for more than five consecutive days) dexamethasone group (n = 274) = 9 placebo group (n = 271) = 11 **p = 0.03** **i.e. statistically significant**
	Changes in signs and symptoms – coma Time to coma clearance (median, days from randomization until observation of a Glasgow coma score of 15 for more

	than two consecutive days) dexamethasone group (n = 274) = 9 placebo group (n = 271) = 11 p = 0.23 i.e. not statistically significant
	Changes in signs and symptoms – paresis Number of patients with hemiparesis at baseline to resolve after 9 months of treatment dexamethasone group = 36 of 48 placebo group = 30 of 37 OR[1] (95% CI) = 0.70 (0.24 to 2.00) p = 0.51 i.e. not statistically significant Number of patients without hemiparesis at baseline to be experiencing hemiparesis after 9 months of treatment dexamethasone group = 14 of 226 placebo group = 11 of 234 OR[1] (95% CI) = 1.34 (0.59 to 3.01) i.e. not statistically significant Number of patients to with paraparesis at baseline to resolve after 9 months of treatment dexamethasone group = 19 of 28 placebo group = 9 of 11 OR[1] (95% CI) = 0.47 (0.08 to 2.63)

	i.e. not statistically significant Number of patients without paraparesis at baseline to be experiencing paraparesis after 9 months of treatment dexamethasone group = 11 of 246 placebo group = 11 of 260 OR[1] (95% CI) = 1.06 (0.45 to 2.49) i.e. not statistically significant
	Relapse Defined by the onset of new focal neurologic signs or a fall in the Glasgow coma score of 2 points or more for two or more days after more than seven days of clinical stability or improvement at any time after randomization Number of patients to experience relapse dexamethasone group = 41 of 274 placebo group = 48 of 271 OR[1] (95% CI) = 0.82 (0.52 to 1.29) i.e. not statistically significant Time to relapse (median, days) dexamethasone group = 41 placebo group = 38 p = 0.12 i.e. not statistically significant
	Adverse events – 'severe' events Defined as any event causing or threatening to cause prolonged hospital stay, disability, or death

	Number of patients to experience a severe event dexamethasone group = 26 of 274 placebo group = 45 of 271 **OR[1] (95% CI) = 0.53 (0.31 to 0.88)** **i.e. statistically significant**
Bibliographic reference	Thwaites GE, Macmullen-Price J, Tran TH et al (2007) Serial MRI to determine the effect of dexamethasone on the cerebral pathology of tuberculous meningitis: an observational study. Lancet Neurology 6(3): 230-6
Length of follow up	9 months after treatment initiation
Outcomes measures and effect size	**Changes in signs and symptoms – tuberculoma** Number of patients to experience a tuberculoma dexamethasone group = 9 of 274 placebo group = 5 of 271 OR[1] (95% CI) = 1.81 (0.60 to 5.46) i.e. not statistically significant
	Changes in signs and symptoms – hydrocephalus Number of patients to experience hydrocephalus dexamethasone group = 10 of 274 placebo group = 7 of 271 OR[1] (95% CI) = 1.43 (0.54 to 3.81) i.e. not statistically significant
Source of funding	Wellcome Trust

Comments	
[1] Odds ratio and 95% confidence interval calculated by reviewer Abbreviations: CI, confidence intervals; CSF, cerebrospinal fluid; E, ethambutol; H, isoniazid; HR, hazard ratio; OR, odds ratio; R, rifampicin; RCT, randomised controlled trial; S, streptomycin; Z, pyrazinamide	

BONE & JOINT, INCLUDING SPINAL, TUBERCULOSIS

1.1.19 Cathro, 1958

Bibliographic reference	Cathro AJM (1958) A clinical trial of prednisolone in bone and joint tuberculosis. East African Medical Journal 35(1): 31-5
Study type	RCT
Study quality	*Appropriate method of randomisation used?* unclear *Allocation concealment used?* unclear *Blinding used?* unclear *Groups comparable at baseline?* details provided are limited, but site of disease varies between the 2 groups: prednisolone group = 7 spinal, 2 knee, 1 hip; antituberculosis chemotherapy alone = 4 hip, 2 knee *Groups received the same care apart from the intervention(s) studied?* yes, although details provided are limited *Groups followed up for an equal and appropriate length of time?* no – not for the full treatment period *Groups comparable for treatment completion and availability of outcome data?* yes, although follow-up not for the full treatment period and therefore completion of antituberculosis chemotherapy could not be assessed

<table>
<tr><td></td><td>Study used precise definitions and reliable measures of outcome?
yes
Population studied is the same as the population of interest?
yes, although details provided are limited
Intervention used is the same as the intervention of interest?
antituberculosis chemotherapeutic regimens lacked rifampicin, pyrazinamide and ethambutol
Have substitute outcomes been used instead of the patient-important outcomes of interest?
yes - response to treatment
Analysis followed the intent-to-treat principle?
yes</td></tr>
<tr><td>Number of patients</td><td>Randomised = 16
prednisolone group = 10
antituberculosis chemotherapy alone group = 6</td></tr>
<tr><td>Patient characteristics</td><td>Inclusion
Active tuberculosis of bone and joint
Baseline
Ages ranged from 4 to 47, with an average of 16 years
<table>
<tr><th></th><th>Prednisolone</th><th>Antituberculosis chemotherapy alone</th></tr>
<tr><td>Site of disease
spinal, n (%)</td><td>
7 (70)</td><td>
0 (0)</td></tr>
</table></td></tr>
</table>

		knee, n (%)	2 (20)	4 (67)
		hip, n (%)	1 (10)	2 (33)
Intervention	*Antituberculosis chemotherapy plus prednisolone* Prednisolone (2 months) adults: 20 mg/day Antituberculosis chemotherapy: isoniazid (600 mg/day in adults) and streptomycin (1 g/day in adults); total duration of antituberculosis chemotherapy unknown Children received proportionally smaller doses according to age All patients received surgery			
Comparison	*Antituberculosis chemotherapy alone* Antituberculosis chemotherapy: isoniazid (600 mg/day in adults) and streptomycin (1 g/day in adults); total duration of antituberculosis chemotherapy unknown Children received proportionally smaller doses according to age All patients received surgery			
Length of follow up	3 months after treatment initiation			
Location	Nairobi, Kenya			
Outcomes measures and effect size	**Response to treatment – need for additional surgical intervention** Number of patients requiring surgery due to insufficient shrinkage of the swollen joint prednisolone group = 9 of 10 antituberculosis chemotherapy alone group = 5 of 6 OR[1] (95% CI) = 1.80 (0.09 to 35.43)			

	i.e. not statistically significant
	Changes in signs and symptoms – weight Number of patients that failed to gain weight prednisolone group = 1 of 10 antituberculosis chemotherapy alone group = 1 of 6 OR[1] (95% CI) = 0.56 (0.03 to 10.93) i.e. not statistically significant
Source of funding	Prednisolone supplied by Pfizer Ltd.
Comments	

[1] Odds ratio and 95% confidence interval calculated by reviewer

Abbreviations: CI, confidence intervals; H, isoniazid; OR, odds ratio; RCT, randomised controlled trial; S, streptomycin

PERICARDIAL TUBERCULOSIS

1.1.20 Hakim et al, 2000

Bibliographic reference	Hakim JG, Ternouth I, Mushangi E et al (2000) Double blind randomised placebo controlled trial of adjunctive prednisolone in the treatment of effusive tuberculous pericarditis in HIV seropositive patients. Heart 84: 183-8
Study type	RCT
Study quality	*Appropriate method of randomisation used?* yes – use of a computer generated randomisation list *Allocation concealment used?* unclear *Blinding used?* double-blind: clinicians and patients were blinded to the identity of the tablets; a randomisation code list was kept sealed and was released at the end of the study *Groups comparable at baseline?* yes *Groups received the same care apart from the intervention(s) studied?* yes *Groups followed up for an equal and appropriate length of time?* yes *Groups comparable for treatment completion and availability of outcome data?* unclear *Study used precise definitions and reliable measures of outcome?*

	yes *Population studied is the same as the population of interest?* yes *Intervention used is the same as the intervention of interest?* yes *Have substitute outcomes been used instead of the patient-important outcomes of interest?* yes – pill counts are a surrogate for adherence; improvement in cardiothoracic ratio and echocardiographic measurement of pericardial fluid are surrogates for improvement in pericardial effusion *Analysis followed the intent-to-treat principle?* unclear
Number of patients	Randomised = 58 prednisolone group = 29 antituberculosis chemotherapy alone group = 29
Patient characteristics	*Inclusion* Age 18–55 years Residence in Harare city to ensure good follow up HIV seropositive No diagnosis of tuberculosis within the past two years Large pericardial effusion on echocardiography (>1 cm anteriorly and >1 cm posteriorly Pericardial aspirate with >50% lymphocytes Protein content >30 g/l

Diagnostic criteria

Patients were admitted into the study on the basis of an echocardiographic demonstration of a large fibrinous pericardial effusion and a clinical diagnosis of tuberculous pericarditis, supported by a high lymphocyte count and a high protein content in the pericardial aspirate

Diagnostic and/or therapeutic pericardiocentesis was undertaken in all patients

The typical two dimensional (cross sectional) echocardiography appearance of tuberculous pericarditis was a thickened pericardium with layers of shaggy echoes lining both visceral and parietal pericardium, but various appearances were observed

Clinical examination and appropriate tests excluded alternative causes of pericarditis

Exclusion

Antituberculous treatment started more than 48 hours before recruitment

Corticosteroid treatment within previous one month

Presence of Kaposi's sarcoma or any other malignancy

Coexisting life threatening disease

Bacterial pneumonia

Pregnancy

Cavitating pulmonary tuberculosis

Other causes of pericardial effusion

Baseline

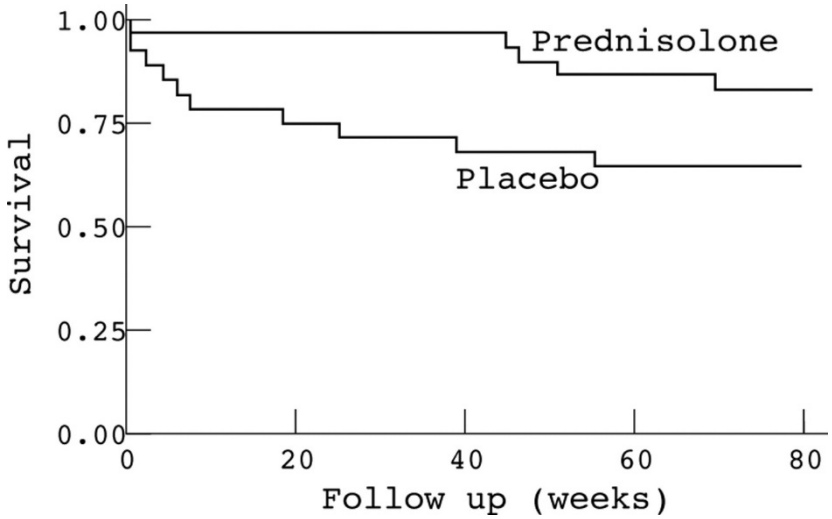
	Prednisolone (n = 29)	**Antituberculosis chemotherapy alone** (n = 29)
Age (mean (range)), years	33 (19–53)	29 (21–41)

Sex, male:female	22:7	18:11
Duration of illness		
unknown	1	1
<2 weeks, n	4	3
2–8 weeks, n	20	15
>8 weeks, n	4	10
Symptoms		
cough, n	27	28
sputum production, n	22	22
haemoptysis, n	6	3
dyspnea		
nil, n	3	5
on exertion, n	16	18
at rest, n	10	6
chest pain, n	26	23
Past medical history		
pneumonia, n	2	2
Signs		
fever (>37.7°C), n	16	18
pulse		
≤100 beats/min	0	0

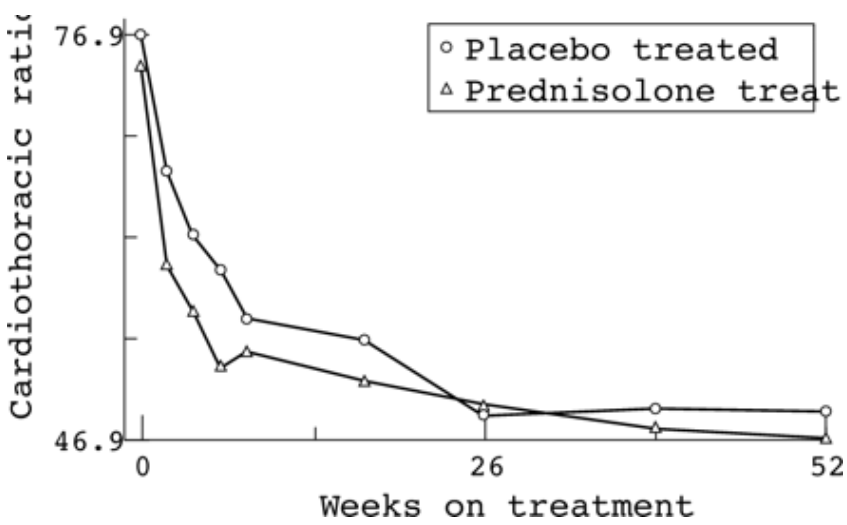
		101–120 beats/min	24	19
		>120 beats/min	5	10
		systolic blood pressure		
		<100 mm Hg	1	2
		≥100 mm Hg	28	27
		pulsus paradoxus	18	16
		jugular venous pressure		
		≤5 cm, n	4	3
		6–10 cm, n	10	14
		>10 cm, n	12	8
		Respiratory rate (mean (range)), /min	29 (18–46)	30 (18–44)
		Weight (mean (range)), kg	57 (42–75)	54 (35–67)
		Oedema		
		nil/just detectable, n	21	18
		affecting legs, n	4	5
		affecting sacrum, n	1	2
		Ascites		
		nil/just detectable, n	26	22
		shifting/dullness, n	1	3
		tense abdomen, n	0	0

		Hepatomegaly		
		≤4 cm, n	7	6
		5–8 cm, n	16	16
		>8 cm, n	4	3
		Patients' perception of wellbeing		
		completely well, n	0	0
		well, but not perfect, n	12	11
		unwell, n	17	17
		Level of physical activity		
		unrestricted, n	11	11
		out and about, but restricted, n	11	12
		restricted to home or hospital, n	6	5
		bedridden, n	1	1
		Haemoglobin <12 g/dl, n	20	19
		Total white cell count <4.0 cells/µl, n	6	1
		Platelet count <100 cells/µl, n	2	1
		CD4+ count (median (IQR))	374 (220–418)	254 (132–352)
		<200 cells/µl, n	3	5
		200–500 cells/µl, n	10	5
		>500 cells/µl, n	2	3
		Liver function tests (median (IQR))		

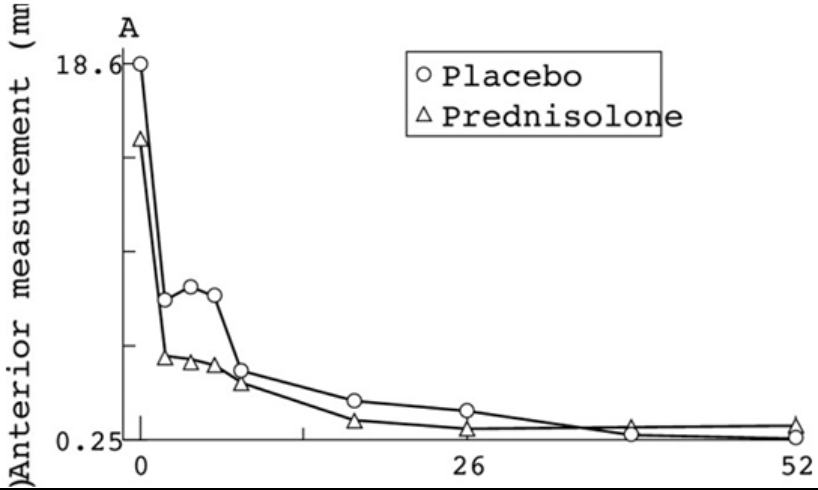
	bilirubin	11 (10–180)	11 (10–27)
	aspartate transaminase	35 (5–520)	32 (6–127)
	alkaline phosphatase	178 (145–361)	237 (100–610)
	albumin	16	12
	Cardiothoracic ratio (chest x-ray)		
	<55%	0	0
	55–75%	9	6
	>75%	5	8
	Low voltage ECG	4	5
	Pericardial effusion size (mean±SD)		
	anterior, cm	2.5±2.1	2.2±1.3
	posterior, cm	2.6±1.0	2.8±1.3
	subcostal,cm	2.7±1.0	2.7±1.0
Intervention	*Antituberculosis chemotherapy plus prednisolone* Prednisolone (6 weeks) starting at a dose of 60 mg (12 tablets) and tapering by 10 mg per week until completion at the end of the sixth week Antituberculosis chemotherapy: 2HRZE/4HR doses not provided		
Comparison	*Antituberculosis chemotherapy plus placebo* Placebo (6 weeks)		

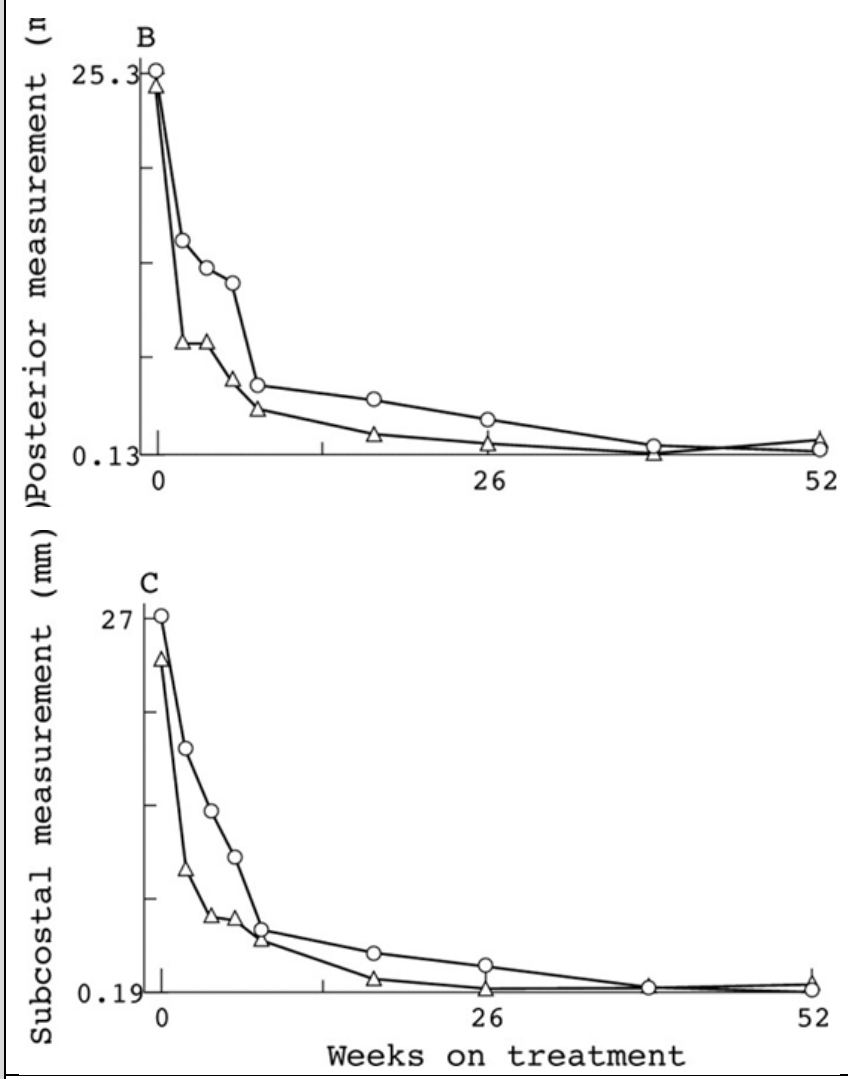
	starting at a dose of 60 mg (12 tablets) and tapering by 10 mg per week until completion at the end of the sixth week Antituberculosis chemotherapy: 2HRZE/4HR doses not provided
Length of follow up	18 months after treatment initiation
Location	Harare, Zimbabwe
Outcomes measures and effect size	**Mortality**  Number of deaths after 18 months prednisolone group = 5 of 29 antituberculosis chemotherapy alone group = 10 of 29 p = 0.004 i.e. statistically significant OR[1] (95% CI) = 0.40 (0.12 to 1.36)

	i.e. not statistically significant
	Changes in signs and symptoms – physical activity Number of patients to experience improvement in physical activity p = 0.017 i.e. statistically significant
	Changes in signs and symptoms – constrictive pericarditis Number of patients to experience constrictive pericarditis prednisolone group = 2 of 29 antituberculosis chemotherapy alone group = 2 of 29 OR[1] (95% CI) = 1.00 (0.13 to 7.62) i.e. not statistically significant
	Changes in signs and symptoms – pericardial effusion Change in cardiothoracic ratio, as measured serially in the prednisolone and placebo treatment groups (p = 0.80, i.e. not statistically significant)[2]



Pericardial fluid regression serial echocardiographic measurements of fluid in the (A) anterior, (B) posterior, and (C) subcostal views (anterior p = 0.19; posterior p = 0.80; subcostal p = 0.39, i.e. not statistically significant)[2]





Adherence

Number of pill counts showing that >90% of tablets had been consumed

	prednisolone group = 169 of 230 antituberculosis chemotherapy alone group = 119 of 182 p = 0.008 i.e. statistically significant OR[1] (95% CI) = 1.47 (0.96 to 2.24) i.e. not statistically significant
Source of funding	CAPS(Pvt) Ltd. provided the prednisolone and placebo tablets and financial support
Comments	

[1] Odds ratio and 95% confidence interval calculated by reviewer

[2] Authors do not specify the statistic used (mean *vs* median etc)

Abbreviations: CI, confidence intervals; E, ethambutol; ECG, echocardiogram; H, isoniazid; IQR, interquartile range; OR, odds ratio; R, rifampicin; RCT, randomised controlled trial; SD, standard deviation; Z, pyrazinamide

1.1.21 Reuter et al, 2006

Bibliographic reference	Reuter H, Burgess LJ, Louw VJ et al (2006) Experience with adjunctive corticosteroids in managing tuberculous pericarditis. Cardiovascular Journal of South Africa 17(5): 233-8
Study type	RCT
Study quality	*Appropriate method of randomisation used?* yes – predetermined randomisation schedule for 100 patients on a 3:3:4 basis; numbers were drawn from a hat, stored on a list on a computer *Allocation concealment used?* yes – randomisation schedule provided to the treating physician with the assigned treatment by a non-clinical administrator

	Blinding used? double-blind: randomisation code remained concealed and was not revealed to the investigators or the study subjects until completion of the study; however, physician administering the intrapericardial steroids/placebo was unblinded *Groups comparable at baseline?* yes *Groups received the same care apart from the intervention(s) studied?* yes *Groups followed up for an equal and appropriate length of time?* yes *Groups comparable for treatment completion and availability of outcome data?* yes *Study used precise definitions and reliable measures of outcome?* yes *Population studied is the same as the population of interest?* yes *Intervention used is the same as the intervention of interest?* yes *Have substitute outcomes been used instead of the patient-important outcomes of interest?* no *Analysis followed the intent-to-treat principle?* yes

<table>
<tr><td>Number of patients</td><td>Randomised = 57
prednisolone group = 16
triamcinolone group = 17
placebo group = 24</td></tr>
<tr><td>Patient characteristics</td><td>Inclusion
Large pericardial effusion on echocardiography (epi-pericardial distance > 10 mm)
Pericardial aspirate with protein content > 30 g/l; (4) pericardial fluid adenosine deaminase (ADA) activity > 35 U/l
Aged 13 to 75 years
Exclusion
CD4 counts <200 cells/µl were excluded due to uncertainty as to the effects of corticosteroids on immunocompromised patients with TB with regard to risk for disseminated disease
Patients presenting with signs of constrictive pericarditis or requiring pericardial surgery within the first 5 days of admission
Baseline
40 of the 57 patients (70.0%) had microbiological and/or histological evidence of TB, the remaining 17 patients (30.0%) were diagnosed by clinical and supportive laboratory data
<table>
<tr><th></th><th>Prednisolone group
(n= 16)</th><th>Triamcinolone group
(n= 17)</th><th>Placebo group
(n= 24)</th></tr>
<tr><td>Sex
female, n
male, n</td><td>
7
9</td><td>
4
13</td><td>
12
12</td></tr>
<tr><td>HIV-seropositive</td><td>9</td><td>6</td><td>6</td></tr>
</table>
</td></tr>
</table>

	Age (mean±SD (range)), years	34.4±9.86 (17–58)	38.6±10.16 (22–66)	33.3±15.86 (17–66)
	Symptoms			
	fever, n (%)	13 (81)	12 (71)	18 (75)
	night sweats, n (%)	7 (44)	7 (41)	10 (42)
	weight loss, n (%)	13 (81)	13 (76)	19 (79)
	anorexia, n (%)	12 (75)	12 (71)	19 (79)
	dyspnea, n (%)	15 (94)	16 (94)	22 (92)
	chest pain, n (%)	6 (38)	4 (24)	7 (29)
	cough, n (%)	14 (88)	15 (88)	20 (83)
	Physical signs			
	lymphadenopathy, n (%)	5 (31)	4 (24)	7 (29)
	soft cardiac sounds, n (%)	13 (81)	14 (82)	20 (83)
	hepatomegaly, n (%)	10 (63)	11 (65)	16 (67)
	peripheral oedema, n (%)	6 (38)	6 (35)	11 (46)
	ascites, n (%)	2 (13)	2 (12)	3 (13)
	tachycardia, n (%)	13 (81)	13 (76)	20 (83)
	pulsus paradoxus, n (%)	3 (19)	5 (29)	7 (29)
	Kassmaul's sign, n (%)	2 (13)	2 (12)	3 (13)
	jugular venous pressure >4 cm, n (%)	13 (81)	15 (88)	20 (83)
	systolic blood pressure <100 mm Hg, n (%)	1 (6)	1 (6)	1 (4)

Intervention 1	*Antituberculosis chemotherapy plus prednisolone* Prednisolone (injection plus 11 weeks) oral prednisone plus intrapericardial placebo (5 ml 0.9% saline solution) intrapericardial placebo: 5 ml 0.9% saline solution oral prednisone: started at 60 mg/day for 4 weeks, followed by 30 mg/day for 4 weeks, 15 mg/day for 2 weeks and 5 mg/day for 1 week Antituberculosis chemotherapy: 2HRZE/4HR doses not provided Patients were discharged on antituberculous therapy and pyridoxine with adjunctive prednisone
Intervention 2	*Antituberculosis chemotherapy plus triamcinalone* Triamcinolone (injection) 200 mg (5 ml) intrapericardial triamcinolone hexacetonide due to limited resources, an oral placebo was not used in conjunction with the intrapericardial triamcinolone Antituberculosis chemotherapy: 2HRZE/4HR doses not provided Patients were discharged on antituberculous therapy and pyridoxine
Comparison	*Antituberculosis chemotherapy plus placebo* Placebo (injection) 200 mg (5 ml) intrapericardial placebo due to limited resources, an oral placebo was not used in conjunction with the intrapericardial placebo

	Antituberculosis chemotherapy: 2HRZE/4HR doses not provided Patients were discharged on antituberculous therapy and pyridoxine
Length of follow up	1 year
Location	Western Cape, South Africa
Outcomes measures and effect size	**Mortality** Number of deaths prednisolone group = 0 of 16 triamcinolone group = 0 of 17 placebo group = 0 of 24 *Any corticosteroid*[1] vs *placebo* OR[2] (95% CI) = 0.73 (0.01 to 38.15) i.e. not statistically significant *Prednisolone*[3] vs *triamcinalone* OR[2] (95% CI) = 2.06 (0.04 to 112.94) i.e. not statistically significant *Prednisolone*[3] vs *placebo* OR[2] (95% CI) = 2.88 (0.05 to 156.88) i.e. not statistically significant
	Response to treatment – need for additional intervention Number of patients to require surgery

	prednisolone group = 2 of 16 triamcinolone group = 0 of 17 placebo group = 0 of 24 *Any corticosteroid*[1] vs *placebo* OR[2] (95% CI) = 3.66 (0.17 to 79.63) i.e. not statistically significant *Prednisolone*[3] vs *triamcinalone* OR[2] (95% CI) = 6.18 (0.23 to 168.11) i.e. not statistically significant *Prednisolone*[3] vs *placebo* OR[2] (95% CI) = 8.65 (0.32 to 233.13) i.e. not statistically significant
	Changes in signs and symptoms – activity levels Number of patients to experience reduced levels of activity at 1-year of follow-up prednisolone group = 2 of 16 triamcinolone group = 2 of 17 placebo group = 3 of 24 *Any corticosteroid*[1] vs *placebo* OR[2] (95% CI) = 0.97 (0.20 to 4.78) i.e. not statistically significant *Prednisolone*[3] vs *triamcinalone*

	OR[2] (95% CI) = 1.07 (0.08 to 13.90) i.e. not statistically significant *Prednisolone*[3] vs *placebo* OR[2] (95% CI) = 1.00 (0.09 to 11.24) i.e. not statistically significant
Source of funding	Crossley Fund and the South African Medical Research Council
Comments	

[1] Data for the 2 corticosteroid groups pooled by reviewer

[2] Odds ratio and 95% confidence interval calculated by reviewer

[3] Data for prednisolone arm split in 2 to allow 2 pairwise comparisons of prednisolone *vs* triamcinolone and prednisolone *vs* placebo

Abbreviations: CI, confidence intervals; E, ethambutol; H, isoniazid; OR, odds ratio; R, rifampicin; RCT, randomised controlled trial; SD, standard deviation; Z, pyrazinamide

1.1.22 Strang et al, 1987/2004

Study type	RCT
Study quality	*Appropriate method of randomisation used?* quasi-randomised: randomised in blocks of by entering names consecutively into a register *Allocation concealment used?* yes *Blinding used?* double-blind; all the clinical, radiographic, bacteriological, echocardiogram and histological data reviewed blind by an independent assessor

	Groups comparable at baseline? yes *Groups received the same care apart from the intervention(s) studied?* yes, although details provided are limited *Groups followed up for an equal and appropriate length of time?* yes *Groups comparable for treatment completion and availability of outcome data?* yes *Study used precise definitions and reliable measures of outcome?* yes *Population studied is the same as the population of interest?* yes *Intervention used is the same as the intervention of interest?* antituberculosis chemotherapeutic regimens lacked ethambutol and contained streptomycin *Have substitute outcomes been used instead of the patient-important outcomes of interest?* yes – favourable response to treatment is a substitute for changes in signs and symptoms; isoniazid metabolites in the urine is a substitute for adherence *Analysis followed the intent-to-treat principle?* yes
Number of patients	Randomised = 143 prednisolone group = 70

	placebo group = 73 Outcome data available at 24 months = 114 prednisolone group = 53 placebo group = 61 Outcome data available at 10 years = 140 prednisolone group = 69 placebo group = 71
Patient characteristics	*Inclusion* Active tuberculous constrictive pericarditis Normal, or only moderately enlarged, cardiac shadow on x-ray 5 years and older *Diagnostic criteria* Reduced physical activity and breathlessness Increased jugular venous pressure Arterial pulsus paradoxus Tachycardia Hepatomegaly Ascites Non-specific but widespread T-wave changes and low voltage QRS complexes on the electrocardiogram Diagnosis considered definitely or probably correct in 136 of 143 patients *Exclusion*

Previous antituberculosis chemotherapy, or antituberculosis chemotherapy for 2 weeks or more during the previous year

Baseline

	Prednisolone group	**Placebo group**
Sex		
males, n (%)	23 (43)	25 (41)
Age		
<15 years, n (%)	1 (2)	1 (2)
15–34 years, n (%)	3 (6)	7 (11)
35–54 years, n (%)	24 (45)	33 (54)
≥55 years, n (%)	25 (47)	20 (33)
Pulse		
≤100/min, n (%)	18 (34)	16 (26)
101–120/min, n (%)	25 (47)	33 (54)
>120/min, n (%)	10 (19)	12 (20)
Paradoxus >10 mm Hg, n (%)	10 (20)	21 (35)
Jugular venous pressure		
≤5 cm, n (%)	2 (4)	6 (10)
6–10 cm, n (%)	25 (47)	24 (39)
>10 cm, n (%)	26 (49)	31 (51)
Liver		

	≤4 cm, n (%)	4 (8)	2 (2)
	5–8 cm, n (%)	33 (62)	29 (48)
	>8 cm, n(%)	16 (30)	30 (49)
	Ascites[1]		
	0–1, n (%)	16 (30)	14 (23)
	2, n (%)	27 (51)	40 (66)
	3, n (%)	10 (19)	7 (11)
	Oedema[2]		
	0–1, n (%)	33 (62)	25 (41)
	2, n (%)	6 (11)	10 (16)
	3, n (%)	14 (26)	26 (43)
	Activity[3]		
	1, n (%)	2 (4)	4 (7)
	2, n (%)	27 (51)	27 (44)
	3, n (%)	15 (28)	13 (21)
	4, n (%)	9 (17)	17 (28)
	Echocardiogram voltage <6 mm in V6 and <4 mm along frontal axis, n (%)	17 (34)	21 (35)
	Cardiothoracic ratio >55%, n (%)	32 (67)	36 (73)
Intervention	*Antituberculosis chemotherapy plus prednisolone*		

Prednisolone (11 weeks)

Age, years	**3x daily for**			**1x daily for week 11**
	weeks 1 to 4 (total daily dose, mg)	**weeks 5 to 8** (total daily dose, mg)	**weeks 9 to 10** (total daily dose, mg)	(total daily dose, mg)
5–9	30	15	7.5	2.5
10–14	45	22.5	7.5	2.5
≥15	60	30	15	5

Antituberculosis chemotherapy: 3HRZS/HR

Weight, kg	**1x daily**			
	Streptomycin (total daily dose, mg)	**Isoniazid** (total daily dose, mg)	**Rifampicin** (total daily dose, mg)	**Pyrazinamide** (total daily dose, mg)
<20	300	150	250	500
20–29	500	250	400	1000
30–39	700	300	450	1500
40–49	900	300	450	1500
≥50	1000	300	600	2000

Every dose given under direct supervision of the hospital staff

Comparison

Antituberculosis chemotherapy plus placebo

Placebo (11 weeks)

Age, years	**3x daily for**			**1x daily for week 11**
	weeks 1 to 4	**weeks 5 to 8**	**weeks 9 to 10**	(total daily dose, mg)

	<table><tr><td></td><td>(total daily dose, mg)</td><td>(total daily dose, mg)</td><td>(total daily dose, mg)</td><td></td></tr><tr><td>5–9</td><td>30</td><td>15</td><td>7.5</td><td>2.5</td></tr><tr><td>10–14</td><td>45</td><td>22.5</td><td>7.5</td><td>2.5</td></tr><tr><td>≥15</td><td>60</td><td>30</td><td>15</td><td>5</td></tr></table> Antituberculosis chemotherapy: 3HRZS/HR <table><tr><td rowspan="2">Weight, kg</td><td colspan="4">1x daily</td></tr><tr><td>Streptomycin (total daily dose, mg)</td><td>Isoniazid (total daily dose, mg)</td><td>Rifampicin (total daily dose, mg)</td><td>Pyrazinamide (total daily dose, mg)</td></tr><tr><td><20</td><td>300</td><td>150</td><td>250</td><td>500</td></tr><tr><td>20–29</td><td>500</td><td>250</td><td>400</td><td>1000</td></tr><tr><td>30–39</td><td>700</td><td>300</td><td>450</td><td>1500</td></tr><tr><td>40–49</td><td>900</td><td>300</td><td>450</td><td>1500</td></tr><tr><td>≥50</td><td>1000</td><td>300</td><td>600</td><td>2000</td></tr></table> Every dose given under direct supervision of the hospital staff
Location	Transkei
Bibliographic reference	Strang JIG, Nunn AJ, Johnson DA (2004) Management of tuberculous constrictive pericarditis and tuberculous pericardial effusion in Transkei: results at 10 years follow-up. Quarterly Journal of Medicine 97: 525-35
Length of follow up	10 years
Outcomes measures and effect size	**Mortality** Number of deaths during 10 years of follow-up prednisolone group = 16 of 70

	placebo group = 21 of 73 OR[4] (95% CI) = 0.73 (0.35 to 1.56) i.e. not statistically significant
	Response to treatment – need for surgical intervention Number of patients to require surgical intervention (pericardeictomy, as indicated by signs of severe constriction despite at least 3 months of antituberculosis chemotherapy) during 10 years of follow-up prednisolone group = 18 of 70 placebo group = 22 of 73 OR[4] (95% CI) = 0.80 (0.39 to 1.67) i.e. not statistically significant
	Changes in signs and symptoms – physical activity Number of patients to with unrestricted physical activity after 10 years of follow-up prednisolone group = 9 of 70 placebo group = 14 of 73 OR[4] (95% CI) = 0.62 (0.25 to 1.55) i.e. not statistically significant Number of patients to be 'out and about' but with restricted physical activity after 10 years of follow-up prednisolone group = 37 of 70 placebo group =32 of 73 OR[4] (95% CI) = 1.44 (0.74 to 2.78) i.e. not statistically significant

	Number of patients to confined to home or hospital after 10 years of follow-up prednisolone group = 5 of 70 placebo group = 2 of 73 OR[4] (95% CI) = 2.73 (0.51 to 14.56) i.e. not statistically significant
Bibliographic reference	Strang JIG, Kakaza HHS, Gibson DG et al (1987) Controlled trial of prednisolone as adjuvant in treatment of tuberculous constrictive pericarditis in Transkei. Lancet 2(8573): 1418-22
Length of follow up	24 months
Outcomes measures and effect size	**Response to treatment – favourable** Defined by the following criteria (or if only 1 were still abnormal): pulse rate of ≤100/min jugular vein pulse of ≤5 cm arterial pulsus paradoxus of ≤10 mm Hg ascites and oedema classified as nil or just detectable physical activity unrestricted cardiothoracic ration of ≤55% echocardiogram voltage of ≥6 mm in V6 or ≥4 mm along the frontal axis Number of patients to be considered in a favourable status after 24 months of follow-up prednisolone group = 50 of 70 placebo group = 52 of 73 OR[4] (95% CI) = 1.01 (0.49 to 2.08)

	i.e. not statistically significant
Source of funding	Grant from the Wellcome Trust; Ciba-Geigy and Gruppo Lepetit provided the rifampicin and the isoniazid; Bracco provided the pyrazinamide; Glaxo provided the prednisolone and the placebo
Comments	

[1] Degree of ascites scored as follows: 0 = nil; 1 = just detectable; 2 = shifting dullness; 3 = tense, distended abdomen

[2] Degree of peripheral oedema scored as follows: 0 = nil; 1 = just detectable; 2 = affecting legs but not sacrum; 3 = affecting legs and sacrum

[3] Degree of physical activity scored as follows: 0 = nil; 1 = activity unrestricted; 2 = out and about but activity restricted; 3 = confined to home or hospital; 4 = bedridden

[4] Odds ratio and 95% confidence interval calculated by reviewer

Abbreviations: CI, confidence intervals; H, isoniazid; OR, odds ratio; R, rifampicin; RCT, randomised controlled trial; S, streptomycin; TB, tuberculosis

1.1.23 Strang et al, 1988/2004

Study type	RCT
Study quality	*Appropriate method of randomisation used?* quasi-randomised: randomised in blocks of by entering names consecutively into a register *Allocation concealment used?* yes *Blinding used?* double-blind; all the clinical, radiographic, bacteriological, echocardiogram and histological data reviewed blind by an independent assessor *Groups comparable at baseline?* unclear

	Groups received the same care apart from the intervention(s) studied? yes, although details provided are limited *Groups followed up for an equal and appropriate length of time?* yes *Groups comparable for treatment completion and availability of outcome data?* yes *Study used precise definitions and reliable measures of outcome?* yes *Population studied is the same as the population of interest?* yes *Intervention used is the same as the intervention of interest?* antituberculosis chemotherapeutic regimens lacked ethambutol and contained streptomycin *Have substitute outcomes been used instead of the patient-important outcomes of interest?* yes – favourable response to treatment is a substitute for changes in signs and symptoms; isoniazid metabolites in the urine is a substitute for adherence *Analysis followed the intent-to-treat principle?* no
Number of patients	Randomised = 240 prednisolone group = 117 placebo group = 123 Outcome data available at 24 months = 198

<table>
<tr><td></td><td>prednisolone group = 97
placebo group = 101
Outcome data available at 10 years = 228
prednisolone group = 112
placebo group = 116</td></tr>
<tr><td>Patient characteristics</td><td>Inclusion
Active tuberculous pericardial effusion confirmed by pericardiocentesis (diagnosis considered definitely or probably correct in 238 of 240 patients)
5 years and older
Exclusion
Previous antituberculosis chemotherapy, or antituberculosis chemotherapy for 2 weeks or more during the previous year</td></tr>
<tr><td>Intervention</td><td>Antituberculosis chemotherapy plus prednisolone
Prednisolone (11 weeks)
<table>
<tr><td rowspan="2">Age, years</td><td colspan="3">3x daily for</td><td rowspan="2">1x daily for week 11
(total daily dose, mg)</td></tr>
<tr><td>weeks 1 to 4
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</table>
Antituberculosis chemotherapy: 3HRZS/HR
<table>
<tr><td>Weight, kg</td><td>1x daily</td></tr>
</table></td></tr>
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<table>
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<tr><td>≥50</td><td>1000</td><td>300</td><td>600</td><td>2000</td></tr>
</table>
Every dose given under direct supervision of the hospital staff

Patients that gave their consent were also randomised to receive complete open surgical drainage or pericardiocentesis</td></tr>
<tr><td>Comparison</td><td>Antituberculosis chemotherapy plus placebo

Placebo (11 weeks)
<table>
<tr><td rowspan="2">Age, years</td><td colspan="3">3x daily for</td><td rowspan="2">1x daily for week 11
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Antituberculosis chemotherapy: 3HRZS/HR
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<tr><td>Length of follow up</td><td>10 years</td></tr>
<tr><td>Outcomes measures and effect size</td><td>Mortality

Number of deaths during 10 years of follow-up

prednisolone group = 26 of 117

placebo group = 33 of 123

OR[4] (95% CI) = 0.78 (0.43 to 1.41)

i.e. not statistically significant

Survival analysis</td></tr>
</table>

Patient group	Variable*		Adjusted HR	95%CI
Constriction ($n=143$)	Treatment	Prednisolone	0.61	0.32–1.19
		Placebo	1.00	
	Age	1-year increase	1.03	1.00–1.06
	Gender	Male	2.80	1.39–5.63
		Female	1.00	
Effusion ($n=175$**)	Treatment	Prednisolone	0.68	0.38–1.24
		Placebo	1.00	
	Age	1-year increase	1.06	1.04–1.09
	Gender	Male	2.72	1.48–5.02
		Female	1.00	
All ($n=318$)	Pericarditis	Constriction	1.00	
		Effusion	1.02	0.66–1.57
	Treatment	Prednisolone	0.64	0.41–0.99
		Placebo	1.00	
	Age	1-year increase	1.05	1.03–1.07
	Gender	Male	2.70	1.71–4.28
		Female	1.00	

* Includes significant predictors and treatment. **One patient allocated to placebo was not included in this analysis because their age was unavailable.

Response to treatment – need for surgical intervention

Number of patients to require surgical intervention during 10 years of follow-up

prednisolone group = 11 of 117

placebo group = 7 of 123

OR[4] (95% CI) = 1.72 (0.64 to 4.60)

i.e. not statistically significant

Changes in signs and symptoms – physical activity

Number of patients to with unrestricted physical activity after 10 years of follow-up

prednisolone group = 21 of 117

	placebo group = 30 of 123 OR[4] (95% CI) = 0.68 (0.36 to 1.27) i.e. not statistically significant Number of patients to be 'out and about' but with restricted physical activity after 10 years of follow-up prednisolone group = 57 of 117 placebo group = 46 of 123 OR[4] (95% CI) = 1.59 (0.95 to 2.66) i.e. not statistically significant Number of patients to confined to home or hospital after 10 years of follow-up prednisolone group = 8 of 117 placebo group = 7 of 123 OR[4] (95% CI) = 1.22 (0.43 to 3.47) i.e. not statistically significant
Bibliographic reference	Strang JIG, Kakaza HHS, Gibson DG et al (1987) Controlled trial of prednisolone as adjuvant in treatment of tuberculous constrictive pericarditis in Transkei. Lancet 2(8573): 1418-22
Length of follow up	24 months
Outcomes measures and effect size	**Response to treatment – favourable** Defined by the following criteria (or if only 1 were still abnormal): pulse rate of ≤100/min jugular vein pulse of ≤5 cm arterial pulsus paradoxus of ≤10 mm Hg

	ascites and oedema classified as nil or just detectable physical activity unrestricted cardiothoracic ration of ≤55% echocardiogram voltage of ≥6 mm in V6 or ≥4 mm along the frontal axis Number of patients to be considered in a favourable status after 24 months of follow-up prednisolone group = 91 of 117 placebo group = 88 of 123 OR[4] (95% CI) = 1.39 (0.77 to 2.50) i.e. not statistically significant
Source of funding	Grant from the Wellcome Trust; Ciba-Geigy and Gruppo Lepetit provided the rifampicin and the isoniazid; Bracco provided the pyrazinamide; Glaxo provided the prednisolone and the placebo
Comments	

[1] Degree of ascites scored as follows: 0 = nil; 1 = just detectable; 2 = shifting dullness; 3 = tense, distended abdomen

[2] Degree of peripheral oedema scored as follows: 0 = nil; 1 = just detectable; 2 = affecting legs but not sacrum; 3 = affecting legs and sacrum

[3] Degree of physical activity scored as follows: 0 = nil; 1 = activity unrestricted; 2 = out and about but activity restricted; 3 = confined to home or hospital; 4 = bedridden

[4] Odds ratio and 95% confidence interval calculated by reviewer

Abbreviations: CI, confidence intervals; H, isoniazid; OR, odds ratio; R, rifampicin; RCT, randomised controlled trial; S, streptomycin; TB, tuberculosis

IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME

1.1.24 Meintjes et al, 2010

Bibliographic reference	Meintjes G, Wilkinson RJ, Morroni C (2010) Randomised placebo-controlled trial of prednisolone for paradoxical tuberculosis-associated immune reconstitution inflammatory syndrome. AIDS 24: 2381-90
Study type	RCT
Study quality	*Appropriate method of randomisation used?* yes – a randomization sequence assigning participants in a 1:1 ratio was generated using Excel by the study statistician and given to an independent pharmacist *Allocation concealment used?* unclear *Blinding used?* double-blind *Groups comparable at baseline?* there was a longer period (p = 0.02) between taking antituberculosis chemotherapy and initiating ART amongst patients in the prednisolone arm (66 days) than the placebo arm (43.5 days) *Groups received the same care apart from the intervention(s) studied?* yes *Groups followed up for an equal and appropriate length of time?* study period only 12 weeks *Groups comparable for treatment completion and availability of outcome data?* yes

	Study used precise definitions and reliable measures of outcome? yes *Population studied is the same as the population of interest?* yes *Intervention used is the same as the intervention of interest?* yes, although patients received streptomycin instead of ethambutol, and some patients did not receive rifampicin *Have substitute outcomes been used instead of the patient-important outcomes of interest?* no *Analysis followed the intent-to-treat principle?* yes
Number of patients	Randomised = 110 prednisolone group = 55 antituberculosis chemotherapy alone group = 55
Patient characteristics	*Inclusion* New or recurrent tuberculosis symptoms and ≥1 of the following TB-IRIS manifestations were enrolled: infiltrate on chest radiograph enlarging lymph node/s serous effusion cold abscess *Exclusion* Age < 18 years

Known rifampicin-resistant tuberculosis

Previous glucocorticoid therapy during this tuberculosis episode

Prior ART exposure, pregnancy

Uncontrolled diabetes mellitus

Kaposi's sarcoma

Immediately life-threatening TB-IRIS, defined as: respiratory failure with arterial pO2 < 8 kPa, altered level of consciousness, new focal neurological sign/s, or compression of a vital structure

Baseline

	Prednisolone (n = 55)	**Placebo** (n = 55)
Age (mean (range)), years	31.5 (19.1–46.0)	31.6 (19.0–56.9)
Sex, male:female	17:38	23:32
Previous tuberculosis, n	15	10
CD4+ count prior to ART (mean (range)), cells/μl	56 (30–103)	48 (20–92)
WHO stage 4 at ART initiation	29	33
Duration antitubercular therapy to ART (mean (range)), days	66 (35–84)	43.5 (23.8-76)
Duration ART to TB-IRIS (mean (range)), days	14 (7–21)	10 (7–19)
Duration TB-IRIS to enrolment (mean (range)), days	12.5 (7–21)	14 (8–23.5)
TB-IRIS manifestations		

	new/recurrent lymphadenopathy, n	19	28
	new/recurrent cold abscess, n	1	1
	new/recurrent pulmonary infiltrate, n	19	16
	new/recurrent serious effusion, n	9	9
	CD4+ count (mean (range)), cells/μl	138 (78–243)	109 (55–190)
	Random glucose (mean (range)), mmol/l	5.1 (4.8–6.0)	5.3 (4.8–5.7)
	Haemoglobin (mean (range)), g/dl	9.1 (8.1–10.3)	9.2 (7.8–10.1)
	Albumin (mean (range)), g/l	23 (20–26)	23 (19.5–26.5)
	C-reactive protein (mean (range)), mg/l	104 (50–150)	106 (79–172)
	Random cortisol (mean (range)), nmol/l	471 (350–614)	559.5 (405.8–774.0)
	Hepatitis B surface antigen positive, n	3/42	3/52
	Weight (mean (range)), kg	51.6 (48.1–56.5)	52.2 (46.6–58.8)
	Hospitalised at enrolment	14	19
	Antibiotics prior to enrolment	25	19
	Karnofsky performance score (mean (range))	70 (30–80)	70 (30–80)
	MOS-HIV health survey		
	physical health summary score	36.3 (33.4–43.1)	37.9 (32.8–44.9)
	mental health summary score	49.7 (44.5–56.0)	49.8 (39.1–56.9)
Intervention	*Antituberculosis chemotherapy plus prednisolone* Prednisolone (4 weeks)		

	1.5mg/kg/day for 2 weeks followed by 0.75mg/kg/day for 2 weeks If significant clinical deterioration occurred after 2 weeks of follow up, the study protocol allowed participants to be switched to open label prednisone Antituberculosis chemotherapy: treatment-naïve: 2HRZE/4HR re-treatment: 2HRZSE/1HRZE/5HRE doses not described
Comparison	*Antituberculosis chemotherapy plus placebo* Placebo (4 weeks) 1.5mg/kg/day for 2 weeks followed by 0.75mg/kg/day for 2 weeks If significant clinical deterioration occurred after 2 weeks of follow up, the study protocol allowed participants to be switched to open label prednisone Antituberculosis chemotherapy: treatment-naïve: 2HRZE/4HR re-treatment: 2HRZSE/1HRZE/5HRE doses not described
Location	Western Cape Province, South Africa
Length of follow up	12 weeks
Outcomes measures and effect size	**Mortality** Number of deaths prednisolone group = 3 of 55 antituberculosis chemotherapy alone = 2 of 55

	OR[1] (95% CI) = 1.53 (0.25 to 9.53) i.e. not statistically significant
	Change in signs and symptoms – improvement/deterioration Symptom response was graded in 1 of 3 categories: deteriorated, no change, or improved/resolved; all patients who developed new TB-IRIS symptoms were graded as 'deteriorated' Number of patients in whom symptoms improved or were resolved after 4 weeks prednisolone group = 44 of 55 antituberculosis chemotherapy alone = 31 of 55 OR[1] (95% CI) = 1.81 (0.72 to 4.50) i.e. not statistically significant Number of patients in whom symptoms deteriorated after 4 weeks prednisolone group = 7 of 55 antituberculosis chemotherapy alone = 9 of 55 OR[1] (95% CI) = 0.75 (0.26 to 2.17) i.e. not statistically significant
	Change in signs and symptoms – chest radiograph Utilized a 3-point scale (deteriorated, no change, or improved/resolved Number of patients in whom chest radiographs were improved or resolved after 4 weeks prednisolone group = 40 of 55 antituberculosis chemotherapy alone = 25 of 55 **OR[1] (95% CI) = 3.20 (1.44 to 7.09)**

	i.e. statistically significant Number of patients in whom chest radiographs were deteriorated after 4 weeks prednisolone group = 4 of 55 antituberculosis chemotherapy alone = 18 of 55 **OR[1] (95% CI) = 0.16 (0.05 to 0.52)** **i.e. statistically significant**
	Adverse events Number of patients in to experience adverse drug reactions prednisolone group = 8 of 55 antituberculosis chemotherapy alone = 3 of 55 OR[1] (95% CI) = 2.95 (0.74 to 11.78) i.e. not statistically significant Number of patients in to experience infections prednisolone group = 27 of 55 antituberculosis chemotherapy alone = 17 of 55 OR[1] (95% CI) = 2.16 (0.99 to 4.70) i.e. not statistically significant
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Comments	

[1] Odds ratio and 95% confidence interval calculated by reviewer

Abbreviations: ART, antiretroviral therapy; CI, confidence intervals; E, ethambutol; H, isoniazid; IRIS, immune reconstitution inflammatory syndrome; OR, odds ratio; R, rifampicin; RCT, randomised controlled trial; S, streptomycin; TB, tuberculosis