

Section 7: Management of Non-Respiratory TB

MGTM1a: In adults with TB meningitis disease, is a standard drug treatment regimen of less than twelve months, as effective as a twelve-month drug treatment regimen in eradicating TB infection?

MGTM1b: In children with TB meningitis disease, is a standard drug treatment regimen of less than twelve months, as effective as a twelve-month drug treatment regimen in eradicating TB infection?

MGTM2: In patients of all ages with TB meningitis disease, do corticosteroids as an adjunct to an anti-tuberculosis drug treatment regimen, decrease morbidity and mortality compared to an anti-tuberculosis drug regimen alone?

MGTO1: In patients with peripheral lymph node TB on drug treatment, are regimens of six months duration as effective as regimens of other durations in eradicating TB infection?

MGTO2: In patients with TB of the spine on drug treatment, are regimens of six months duration as effective as regimens of longer durations in eradicating TB infection?

MGTO3: In patients with TB of the spine, is surgery (anterior spinal fusion) with short course chemotherapy more effective than short course chemotherapy alone in eradicating TB infection?

MGTO4: In patients with TB pericarditis on drug treatment, are regimens of six months duration as effective as regimens of longer durations in reducing mortality and morbidity?

MGTO5: In patients with TB pericarditis, are corticosteroids in addition to drug treatment, effective in reducing mortality and morbidity compared to drug treatment alone?

Evidence Table	
MGTM1a: In adult patients with TB meningitis disease, is a standard drug treatment regimen of less than twelve months, as effective as a twelve month drug treatment regimen in eradicating TB?	
Author / title / reference / yr	Doganay, M., Calangu, S., Turgut, H., Bakir, M., & Aygen, B. 1995, "Treatment of tuberculous meningitis in Turkey", <i>Scandinavian Journal of Infectious Diseases.</i> , vol. 27, no. 2, pp. 135-138.
N=	N=72 Setting: The study was carried out at 4 university clinics in Turkey. Three clinics studied short-course chemotherapy and one used long-course therapy.
Research design	Cohort study
Aim	The authors state that the aim of the study was to evaluate the results of therapy in cases of TB meningitis at four centres in Turkey. They report results from short-course chemotherapy (8 months) and longer course chemotherapy (12 to 16 months).
Population	Patients over 15 years old with diagnosed TB meningitis were enrolled in the study. Diagnosis was based on the following: <ol style="list-style-type: none"> 1) clinical findings of subacute and chronic meningitis (meningeal symptoms lasting for >4days); 2) cerebrospinal fluid findings – clear or xanthochromic, elevated cell count with predominance of lymphocytes, glucose level <400mg/l, protein level > 1g/l; 3) demonstration of acid-fast bacilli in CSF by microscopic examination and /or culture; 4) evidence of any associated extrameningeal TB lesion. Patients dying within 5 days of admission were not evaluated. Additionally, patients were excluded from short-course chemotherapy if they were given a different antituberculous regimen for > 1 week or if therapy lapsed for 10 days during the treatment period, or if the patient had been treated for TB in the last 2 years.
Intervention	N=37 on 8 month treatment (short course chemotherapy). Short course chemotherapy was a combination of isoniazid (300mg/day), rifampicin (600mg/day), pyrazinamide (1500mg/day) and streptomycin (1g daily for a months thereafter on alternate days to a total of 45mg) for 2 months followed by a combination of isoniazid (300mg /day), and rifampicin (600mg/day) for 6 months. Prednisolone was initially given for 4 or 6 weeks to patients in stage III of the short course group.
Comparison	N=35 on treatment for 12 to 16 months (long course chemotherapy). Long course chemotherapy included 4 antituberculous drugs initially for 4-6 months followed by a combination of 3 or 4 drugs.

	<p>N=19 patients were given a combination of isoniazid, rifampicin, pyrazinamide and ethambutol N=6 received a combination of isoniazid, rifampicin, streptomycin and ethambutol N=6 received a combination of isoniazid, rifampicin, streptomycin and pyrazinamide. N=3 received a combination of isoniazid, rifampicin, streptomycin pyrazinamide and ethambutol. N=1 received a combination of isoniazid, rifampicin and ethambutol Protainamide was also given to 3 patients. No rationale is given for the choice of therapy in these cases. Prednisolone or dexamethasone was given in the presence of papilloedema, cranial nerve palsies, clouding of consciousness and/or coma in the long course group.. Pyridoxine (100 mg/day) was added to all regimens.</p>																																				
Outcome	The outcomes are number of patients who completed treatment, died, had side effects and recovered with or without sequelae.																																				
Characteristics	<p>Baseline characteristics for the two groups are not reported separately.</p> <table border="1"> <thead> <tr> <th colspan="2">Characteristics of cases</th> </tr> </thead> <tbody> <tr> <td>Number of patients</td> <td>72</td> </tr> <tr> <td>Age (mean ±SD)</td> <td>30.4±2.1</td> </tr> <tr> <td>Sex:</td> <td></td> </tr> <tr> <td> Female</td> <td>32 (44%)</td> </tr> <tr> <td> Male</td> <td>40 (56%)</td> </tr> <tr> <td>Meningitis only</td> <td>38 (53%)</td> </tr> <tr> <td> Meningitis + extrameningeal lesion</td> <td>34 (47%)</td> </tr> <tr> <td> Miliary TB</td> <td>5 (7%)</td> </tr> <tr> <td> Pulmonary TB</td> <td>22 (31%)</td> </tr> <tr> <td> Spondylitis</td> <td>4 (6%)</td> </tr> <tr> <td> Intracerebral tuberculoma</td> <td>1 (1%)</td> </tr> <tr> <td> TB lymphadenitis</td> <td>1 (1%)</td> </tr> <tr> <td> Previous history TB</td> <td>3 (4%)</td> </tr> <tr> <td>Clinical stage:</td> <td></td> </tr> <tr> <td> I</td> <td>7 (10%)</td> </tr> <tr> <td> II</td> <td>34 (47%)</td> </tr> <tr> <td> III</td> <td>31 (43%)</td> </tr> </tbody> </table>	Characteristics of cases		Number of patients	72	Age (mean ±SD)	30.4±2.1	Sex:		Female	32 (44%)	Male	40 (56%)	Meningitis only	38 (53%)	Meningitis + extrameningeal lesion	34 (47%)	Miliary TB	5 (7%)	Pulmonary TB	22 (31%)	Spondylitis	4 (6%)	Intracerebral tuberculoma	1 (1%)	TB lymphadenitis	1 (1%)	Previous history TB	3 (4%)	Clinical stage:		I	7 (10%)	II	34 (47%)	III	31 (43%)
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	<ul style="list-style-type: none"> • Five (14%) patients died in the short course group and 2 (6%) in the long course group. • Of the patients who died in the short-course group, 3 were admitted in clinical stage III and 2 in stage II. Cause of death was respiratory failure (N=2), hydrocephalus (N=1), meningoencephalitis (N=1), and sepsis arachnoidit (N=1). Two deaths in the long-course group were both in stage III patients, one due to cardiac arrest and the other due to therapeutic failure. • Side effects were observed in 6 (16.2%) patients in the short-course group and 8 (22.8%) in the long course group. Toxic hepatitis was observed in 10 cases, nausea and vomiting in 2 and hearing loss in 2. • Residual sequelae developed in 18/58 (31%) patients who survived and were evaluated; of those, 8 (30.7%) were in the short-course group and 10 (31.2%) were in the long-course group. Hemiparesis/ monoparesis persisted in 8 cases, visual impairment in 4, imbalance in 3 and hydrocephalus in 3. Other sequelae were less frequently observed. • 48 cases were followed up after completion of the therapy with a mean duration of 10 months in the short course group (range 6-24) and 13 months in the long-course group (range 4-36). No relapse was observed in either group.
SIGN quality rating	-
Evidence hierarchy grading	2-
Comments	<ul style="list-style-type: none"> • The authors note that “the results were not compared in the 2 therapy groups because the cases could not be randomised”. They do however report separate outcomes for the two groups. Unfortunately, because the baseline characteristics of the two groups have not been presented, it is extremely difficult to interpret these outcomes. • Ten patients (14%) were lost to follow-up. • Patients in the long course chemotherapy group received a variety of different combinations of treatment and the proportion of patients receiving corticosteroid treatments across the groups is likely to differ. • How sequelae was measured is not defined and it is also not apparent how cause of death was established. • No statistical tests have been performed.
NCC CC ID	198

Evidence Table				
MGTM1a: In adult patients with TB meningitis disease, is a standard drug treatment regimen of less than twelve months, as effective as a twelve month drug treatment regimen in eradicating TB?				
Author / title / reference / yr	Phuapradit, P., Vejjajiva, A., Chopra JS, E., Jagannathan, K., & Sawhney IMS, E. 89 A.D., "Short-course chemotherapy for tuberculous meningitis", Advances in neurology: proceedings of the XIVth World Congress of Neurology 1990 pp. 293-298.			
N=	N=52 Setting: Patients were admitted to Ramathibodi Hospital, Bangkok, Thailand.			
Research design	Cohort study with historical control			
Aim	To compare the results of a nine month course of chemotherapy for TB meningitis with a six month course.			
Population	Consecutive patients admitted with TB meningitis. All patients presented with lymphocytic meningitis with low cerebrospinal fluid (CSF) glucose and raised CSF protein concentrations.			
Intervention	N=32 Group I: on a 9 month course of chemotherapy (Immediate treatment with isoniazid 300mg, rifampicin 600mg (400mg for those who weighted less than 45kg), pyrazinamide 1500mg and intramuscular streptomycin 750 to 1000 mg daily as single doses for first two months, followed by isoniazid 300mg and rifampicin 600mg daily for 7 months). Prednisolone 60mg per day was given in a tapering course over 4 to 6 weeks in patients with hydrocephalus, arteritis and arachnoiditis.			
Comparison	N=20 Group II: on a 6 month course of chemotherapy (The same regimen of treatment for the first 2 months as group I; but for the remaining 4 months isoniazid, rifampicin and pyrazinamide at the same doses were given). Prednisolone 60mg per day was given in a tapering course over 4 to 6 weeks in patients with hydrocephalus, arteritis and arachnoiditis.			
Outcome	Number of patients who recovered (survived). Number of patients who fully recovered. Number of deaths. Number of patients with neurological deficits. Recurrence.			
Characteristics	Clinical details	Group I	Group II	

		(N=32)	(N=20)	
	Male:female (%)	53:47	55:45	
	Age range (yrs)	17-76	15-69	
	Mean age (yrs)	33	40	
	CSF+ve for AFB	14 (44%)	4 (20%)	
	Pulmonary TB	20 (62%)	9 (45%)	
	Caseating lymphadenitis	5 (16%)	3 (15%)	
	TB otitis media	2 (6%)	0 (0%)	
	Neurological complications	Group I (N=32)	Group II (N=20)	
	Increased intracranial pressure	23 (72%)	18(90%)	
	Communicating hydrocephalus	12 (38%)	7 (35%)	
	Cranial nerve palsy	8 (25%)	8 (40%)	
	Diffuse cerebral oedema	4 (13%)	0 (0%)	
	Cerebral infarct from arteritis	4 (13%)	6 (30%)	
	Optochiasmatic arachnoiditis	1 (3%)	1 (5%)	
	Spinal arachnoiditis	1 (3%)	2 (10%)	
	Clinical grade (Gordon's & Parson's system)	Group I (N=32)	Group II (N=20)	
	1	4 (12%)	4 (20%)	
	2	21(66%)	14 (70%)	
	3	7 (23%)	2 (10%)	
	(NB Grade 1: patients were conscious and rational with meningism but no focal neurological signs or signs of hydrocephalus. Grade 2: the patients were confused or had focal signs such as squint or hemiparesis. Grade 3: the patients mental state could not be assessed because of stupor or delirium, complete hemiplegia or paraplegia).			
Results	Treatment results and grading			
	Group	Grade	No. Lost to study	No. "recovered" No. died

			(survived)	
I	1	1	3	0
	2	2	19	0
	3	1	4	2
Total		4 (13%)	26 (81%)	2 (6%)
II	1	0	4	0
	2	0	14	0
	3	0	2	0
Total		0 (0%)	20 (100%)	0 (0%)

- In group I, all of the grade 1 and 2 patients had recovered within 2 to 12 weeks.
- In group I, 2 of the grade 3 patients who had severe hydrocephalus on admission did not improve in spite of treatment with early CSFshunting, corticosteroid and assisted ventilation. They remained in a vegetative state and died in the hospital of pressure sores and aspiration pneumonia seven and nine months after the start of treatment respectively. The CFS cultures of these patients grew mycobacterium tuberculosis. Autopsies revealed minimal fibrosis of the basal meninges and cerebral infarcts, but no evidence of tuberculosis infection in the nervous system and other organs.
- In group II, 17 patients completed the 6 month course. The authors note that 3 patients all who were in grade 3 (although the table only has 2 patients in group II who are grade 3) developed tuberculomas at 2, 3 and 4 months after the start of treatment and the chemotherapy had to be continued for 13, 15 and 17 months when computerised tomography (CT) scanning of the brain showed disappearance of the tuberculoma.
- In group I, 26 patients were followed up for a mean 42.4 months after treatment completion (range 12-60 months) and in group II follow up was a mean 20.8 months (range 3-38 months).
- 23 patients (72%) in group I and 15 patients (75%) in group II had full recovery.
- Of the 26 patients followed up in group I, 3 patients had residual neurological deficits, consisting of mild sensori-neural hearing and slight ataxia of gait. There was no reoccurrence of meningitis or of the associated pulmonary TB.
- In group II, of the 17 patients to complete the 6 month treatment (thus excluding the 3 patients who developed tuberculomas and were treated for longer) 2 patients had residual hemiplegia and arrested hydrocephalus. There was no recurrence in this these 17 patients

SIGN quality rating	-
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Evidence hierarchy grading	2-
Comments	<ul style="list-style-type: none"> • There may be confounding factors influencing outcomes. For example, prednisolone was given to differing proportions of patients in each group (38% in group I and 55% in group II), the two chemotherapy regimens were slightly different for each treatment group, follow-up was shorter in the 6-month treatment group so some outcomes may not yet have become apparent, the two groups were not studied concurrently thus the issue of change over time may have been a factor and finally the two groups were not similar at baseline. • Numbers in the study are small. There has been no power calculation and tests of statistical significance have not been performed. • The accuracy of the diagnostic criteria used is questionable. • How sequelae was measured is not defined. • All percentages are calculated by the reviewer as only patient numbers are presented in original paper. • The authors conclude that “intensive chemotherapy of TB meningitis in a majority of patients can shorten the duration of treatment to six months with a favourable outcome”.
NCC CC ID	812

Evidence Table	
MGTM1a: In adult patients with TB meningitis disease, is a standard drug treatment regimen of less than twelve months, as effective as a twelve month drug treatment regimen in eradicating TB?	
Author / title / reference / yr	Chotmongkol, V. 1991, "Treatment of tuberculous meningitis with 6-month course of chemotherapy", <i>Southeast Asian Journal of Tropical Medicine & Public Health.</i> , vol. 22, no. 3, pp. 372-374.
N=	N=29 Setting: Srinagarind Hospital, Khon Kaen, Thailand.
Research design	Case series
Aim	To review the results of short-course chemotherapy (6 months) in adult patients with TB meningitis.
Population	Consecutive patients with a diagnosis of TB meningitis, diagnosed according to the characteristic clinical features and typical cerebrospinal fluid findings (lymphocytic meningitis with low glucose level and elevation of protein content).
Intervention	Oral isoniazid 300mg, rifampicin 600mg (450mg for those who weighted less than 45kg), pyrazimide 1500mg and intramuscular streptomycin 750mg per day as single dose for the first two months followed by isoniazid and rifampicin in the same dose for four months. In patients who could not take streptomycin, ethambutol 800mg was used as a replacement. Prednisolone 45-60 mg per day was given in some patients with mental change, high CSF protein content and spinal arachnoiditis. The dose was gradually tapered off over 2-4 weeks.
Comparison	No comparison
Outcome	Number of patients with recovery. Number of patient deaths. Neurological deficits. Treatment completion.
Characteristics	Age ranged from 16-61 years with a mean of 35 years. Using the Gordon and Parson's severity classification system: N=7 Stage 1 (conscious and rational with meningism but no focal neurological signs or signs of hydrocephalus) N=12 Stage 2 (confused or had focal neurological signs such as squint, hermparesis or signs of hydrocephalus). N=10 Stage 3 (In stage 3 the patient's mental state could not be assessed because of stupor or delirium, complete hemiplegia or paraplegia).

	<table border="1"> <tr> <th colspan="2">Neurological complications in the 29 patients</th> </tr> <tr> <th>Complication</th> <th>Number effected</th> </tr> <tr> <td>Increased intracranial pressure</td> <td>22/29 (76%)</td> </tr> <tr> <td>Communicating hydrocephalus</td> <td>7/18* (39%)</td> </tr> <tr> <td>Cranial nerve palsy</td> <td>3/29 (10%)</td> </tr> <tr> <td>Impaired vision</td> <td>1/29 (3%)</td> </tr> <tr> <td>Spinal arachnoiditis</td> <td>3/29 (10%)</td> </tr> <tr> <td>Tuberculoma</td> <td>4/18* (22%)</td> </tr> <tr> <td>Hemiplegia</td> <td>1/29 (3%)</td> </tr> </table> <p>* CT scans were not performed in 11 patients</p> <p>Abnormal x-ray was observed in 10 patients. Three cases had other foci of TB (peritonitis, osteomyelitis and laryngitis). Mean CSF cell count was 315 cells/mm³ and protein content was 493 mg%. <i>Mycobacterium tuberculosis</i> were positive in 6 patients.</p>	Neurological complications in the 29 patients		Complication	Number effected	Increased intracranial pressure	22/29 (76%)	Communicating hydrocephalus	7/18* (39%)	Cranial nerve palsy	3/29 (10%)	Impaired vision	1/29 (3%)	Spinal arachnoiditis	3/29 (10%)	Tuberculoma	4/18* (22%)	Hemiplegia	1/29 (3%)																		
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Results	<table border="1"> <tr> <th colspan="6">Treatment Results</th> </tr> <tr> <th>Stage on admission</th> <th>No of patients</th> <th>No. of patients lost to study</th> <th>No. of patients with recovery</th> <th>No. of patients who died</th> <th>No. of patients with drug intolerance</th> </tr> <tr> <td>1</td> <td>7</td> <td>2</td> <td>5</td> <td>0</td> <td>0</td> </tr> <tr> <td>2</td> <td>12</td> <td>1</td> <td>9</td> <td>1</td> <td>1</td> </tr> <tr> <td>3</td> <td>10</td> <td>1</td> <td>6</td> <td>3</td> <td>0</td> </tr> <tr> <td>Total</td> <td>29</td> <td>4 (14%)</td> <td>20 (69%)</td> <td>4 (14%)</td> <td>1 (3%)</td> </tr> </table> <ul style="list-style-type: none"> • Twenty-six patients received streptomycin in the first 2 months of treatment and prednisolone was administered in 9 patients. • Twenty patients had complete treatment and of these 15 had immediate CSF studies after treatment completion. Nine cases were within normal limits. Of the remaining 6 cases, 5 had mild elevation of protein content (55-137mg%), mean 93.6mg%) and 1 had mild pleocytosis (8 cells/mm³). Only one case had severe hepatitis due to isoniazid and treatment was continued with rifampicin and ethambutol for 18 months with full recovery. • Of the 4 patients who died (14%), 3 (10%) died from underlying disease and hospital acquired 	Treatment Results						Stage on admission	No of patients	No. of patients lost to study	No. of patients with recovery	No. of patients who died	No. of patients with drug intolerance	1	7	2	5	0	0	2	12	1	9	1	1	3	10	1	6	3	0	Total	29	4 (14%)	20 (69%)	4 (14%)	1 (3%)
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	<p>infection. In the remaining case, symptoms of meningitis improved but the patient died from an infected shunt.</p> <ul style="list-style-type: none"> • During follow-up, 20 patients were observed for 4 to 33 months (mean 16.3 months) after completion of treatment and no recurrence of meningitis was observed. Three of these patients had residual neurological deficits, consisting of visual impairment, spastic hemiplegia with mental impairment and mild lateral rectus muscle palsy. • Four cases who were lost to the study (received anti-tuberculosis drugs for about 2,2,3 and 4 months) all had good recovery with a mean duration of 16.5 months after treatment as indicated by letters. • By inference from the results given it can be calculated that of 20 patients who survived and completed treatment, 3 had neurological deficits and thus 17/29 (58%) patients achieved good recovery on the treatment regimen. This increases in 21/29 (72%) if those lost to follow up are included.
SIGN quality rating	No level 3 critical appraisal checklist available.
Evidence hierarchy grading	3
Comments	<ul style="list-style-type: none"> • “Recovery” used here seems to be synonymous with “survival”. • The authors do not indicate how underlying cause of death was determined. • In diagnosing meningitis TB, low glucose levels and elevated protein content are not defined. • There is no indication of how neurological deficits were assessed. • The authors concluded that “The present study demonstrated that a 6 month regimen of antituberculous drugs was effective, with good results and minimal toxic effects”.
NCC CC ID	200

Evidence Table	
MGTM1a: In adult patients with TB meningitis disease, is a standard drug treatment regimen of less than twelve months, as effective as a twelve month drug treatment regimen in eradicating TB?	
Author / title / reference / yr	Alarcon, F., Escalante, L., Perez, Y., Banda, H., Chacon, G., & Duenas, G. 1990, "Tuberculous meningitis. Short course of chemotherapy", <i>Archives of Neurology.</i> , vol. 47, no. 12, pp. 1313-1317.
N=	N=28 patients Setting: Department of Neurology, Eugenio Espejo Hospital, Ecuador.
Research design	Case series
Aim	To review the clinical and therapeutic characteristics of the short course of treatment (6 months) in 28 cases of TB meningitis.
Population	TB meningitis patients diagnosed by analysis of cerebrospinal fluid; protein and glucose levels; acid-fast bacilli, test culture in Lowenstein-Jensen medium; immunobiological study by enzyme linked immunosorbent assay for detecting anti-bacille Calmette-Guerin (BCG) antibodies and the dosification of adenosine deaminase activity.
Intervention	Oral administration of isoniazid (10mg/kg per day), rifampin (15mg/kg per day), and pyrazinamide (30mg/kg per day). The first phase, which lasted 2 months, included isoniazid, rifampin and pyrazinamide and the second phase, which lasted 4 months was carried out with isoniazid and rifampin. All patients received pyridoxine (50 to 100mg/d). Steroid therapy with prednisolone was indicated for patients with impairment of consciousness, focal neurological abnormalities, and a cerebrospinal fluid pressure of more than 300mm H ₂ O, with the dose being tapered at the beginning of the second or third week until the drug was completely withdrawn.
Comparison	No comparison.
Outcome	Number of patient deaths, full recovery, recovery with neurological sequelae.
Characteristics	75% male and 25% female. Mean age was 29.1 ± 19.4 years (range 11 months to 70 years). N=7 (25%) were children ≤15 years. Diagnostic categories: N=22 definite TB meningitis (when the diagnosis was based on autopsy findings and /or when the cerebrospinal fluid smear and culture for acid-fast bacilli were positive) N=6 probable TB meningitis (when the cerebrospinal fluid smear and culture for acid-fast bacilli were negative but direct films and/ or cultural identification of Mycobacterium tuberculosis were positive from another tissue or body fluids and/or the enzyme-linked immunosorbent assay and/or the

	<p>adenosine deaminase activity in the cerebrospinalfluid were positive and at least two of the following tests were positive: Mantoux test, chest roentgenogram, computed tomographic scanning and a history of, or contact with TB).</p> <p>British Research Council Clinical Stage on admission: Clinical Stage 1 N=8 (29%) Clinical Stage 2 N=6 (21%) Clinical Stage 3 N=14 (50%)</p> <p>British Research Council Clinical Stage at start of treatment: Clinical Stage 1 N=4 (14%) Clinical Stage 2 N=10 (36%) Clinical Stage 3 N=14 (50%)</p> <p>(Those at stage I disease are fully conscious and have no pareses, those at stage II are stuporous and may have focal neurological signs or hemiparesis, and those at stage III are comatose or have a complete hemiplegia or quadriplegia).</p>
Results	<ul style="list-style-type: none"> • 13 patients began treatment on admission (4 in stage 1 and 9 in stage 2 at start of treatment) • 15 patients began treatment after admission (1 in stage 2 and 14 in stage 3 at start of treatment) • Nine patients (32.1%) all classified as stage 3 at the beginning of treatment died. Mortality increased significantly (P<0.005) when treatment was begun at stage 3. • Details of the patient deaths were that one died during a relapse 3 months after having concluded the 6 months of treatment, 6 patients died before completing the second week of treatment, one died 45 days after commencing treatment and another 68 days after beginning treatment. • The mean age of the deceased patients was 40.7 ± 17.1 years whereas for the patients who did not die, it was 24.4 ± 18.6 years (P<0.005). None of the deaths were in children. • Of the 15 patients who received treatment after admission, 3 began treatment on the first day, 4 on the second day, 2 the third day and the remaining 6, between the fourth and seventh days after admission. Of those nine patients who died, six (66.6%) had begun treatment after the third day of admission (P<0.001). • Eighteen months after concluding treatment, three patients (16% of those who survived) displayed neurological sequelae. One patient had mild mental impairment and hemiparesis, one had mild mental impairment and one had behavioural problems and epilepsy. • 16 (57%) patients survived without neurological sequelae.
SIGN quality rating	No level 3 critical appraisal checklist available.
Evidence hierarchy grading	3

Comments	<ul style="list-style-type: none"> • Patients were mostly male. • There is no indication of how neurological deficits were assessed. • The authors conclude that “early onset of antituberculous therapy is more important than the regimen of drugs applied or the duration of the treatment” however they comment that “this short-term scheme is a good therapeutic option because it is effective and displays a morbidity and mortality rate that is comparable with other therapeutic regimens”. • NB: The age range included spans both children and adults however only 25% of the group were children.
NCC CC ID	201

Evidence Table	
MGTM1a: In adult patients with TB meningitis disease, is a standard drug treatment regimen of less than twelve months, as effective as a twelve month drug treatment regimen in eradicating TB?	
Author / title / reference / yr	Acharya, V. N., Kudva, B. T., Retnam, V. J., & Mehta, P. J. 1985, "Adult tuberculous meningitis: comparative study of different chemotherapeutic regimens", <i>Journal of the Association of Physicians of India.</i> , vol. 33, no. 9, pp. 583-585.
N=	N=102 patients in four study arms, however only treatment in one study arm (Group D) included treatment with a combination of isoniazid, rifampicin and pyrazinamide (HRZ). N=20 in Group D. Setting: Department of Medicine, KEM hospital, Bombay.
Research design	Case series (due to exclusion of other study arms)
Aim	To compare different chemotherapeutic regimens in a consecutive series of adult TB meningitis patients
Population	Adult TB meningitis patients diagnosed by CSF pleocytosis, raised CSF proteins with low/low to normal CSF sugar, positive CSF smear and culture for acid fast bacilli, presence of other neural or extra neural TB, therapeutic response to anti-tuberculosis drugs in the presence of a high clinical index of suspicion. At least four of these criteria had to be met in each case.
Intervention	In Group D the intervention was streptomycin (25mg/kg), isoniazid (10mg/kg), rifampicin (10mg/kg) and pyrazinamide (35mg/kg) for 2 months followed by isoniazid and rifampicin (both at 10mg/kg) for 7months. Prednisolone was used at 30mg/day initially and then 5mg/day as maintenance therapy.
Comparison	No comparisons reported here as the other groups did not include HRZ.
Outcome	Cytological response in weeks (percentage of disappearance of lymphocytes in CSF) Clinical response in weeks (percentage of amelioration of symptoms and signs). Time to occurrence of neurological sequelae. (For the first 2 outcomes the responses were quantified after assigning a point to each symptom and sign with the aid of a computer. The response was said to be good with a score of 90% and above, fair when 89 to 50% and poor when less than 50%. The cut-off point of the response in time was considered when maximum response could be judged from the data collected).
Characteristics	Age range 18-30 years (mean 24.7 ± 1.1) Male to female ratio 3:1. Patients were randomly assigned to the four groups however baseline characteristics are not reported

	separately for each group.
Results	<p>In Group D:</p> <ul style="list-style-type: none"> • Follow-up after completion of therapy was mean 8 ± 1.2 months and during this time there was no occurrence of neurological sequelae. • The mean time to cytological response was 2 ± 0.03 weeks. • The mean time to clinical response was 3 ± 0.10 weeks.
SIGN quality rating	No level 3 critical appraisal checklist available.
Evidence hierarchy grading	3
Comments	<ul style="list-style-type: none"> • The number of deaths, clinical stage of the patients and relapse is not reported. • The randomisation process is not described. • Unclear how cytological and clinical responses are measured although these may be considered to be surrogate outcomes.
NCC CC ID	825

Evidence Table	
MGTM1b: In children with TB meningitis disease, is a standard drug treatment regimen of less than 12 months, as effective as a 12 month drug treatment regimen in eradicating TB?	
Author / title / reference / yr	Loenhout-Rooyackers, J. H., Keyser, A., Laheij, R. J., Verbeek, A. L., & van der Meer, J. W. 2001, "Tuberculous meningitis: is a 6-month treatment regimen sufficient?", <i>International Journal of Tuberculosis & Lung Disease.</i> , vol. 5, no. 11, pp. 1028-1035.
N=	N=4 studies (N= 197 patients) included in the 6-months treatment group: Chotmongkol 1991, Alarcon 1990, Jacobs 1992 and Donald 1998 N=5 studies (N= 1176 patients) included in the more than 6-months treatment group: Doganay 1995, Phuapradit 1987, Goel 1990, Humphries 1990 and Ramachandran 1986 and 1989 (studies by Ramachandran of the same population).
Research design	Systematic review.
Aim	To establish whether a 6-month treatment regimen for tuberculous meningitis is equally as effective as longer treatment.
Population	Study populations of patients with TB meningitis in whom the diagnosis was confirmed with clinical, cerebrospinal fluid and epidemiological findings. Patients had to be classified according to the clinical severity of their disease due to its importance to prognosis. Studies had to have at least 12 months follow-up after treatment completion and were required to contain information about CSF analysis and number of relapses.
Intervention	A treatment regimen with at least isoniazid, pyrazinamide and rifampicin (HRZ) in patients treated for 6 months.
Comparison	A treatment regimen with at least isoniazid, pyrazinamide and rifampicin (HRZ) in patients treated for more than 6 months.
Outcome	Relapse rates Death Cure Residual neurological deficits.

Characteristics		6 months treatment	More than 6 months treatment
	Number of studies		4
Number of patients		197	1176
Number analysed		197	675
Age:			
< 16 years		147 (75%)	515 (76%)
≥16 years		50 (25%)	160 (24%)
Diagnosis:			
Clinical stage I		27 (14%)	138 (18%)
Clinical stage II		95 (48%)	434 (58%)
Clinical stage III		75 (38%)	178 (24%)
CSF testing			
Ziehl-Neelsen: positive/ no of specimens		17/61 (28%)	36/103 (35%)
Lowenstein-Jensen: culture positive/ no of specimens		45/187 (24%)	105/330 (32%)
Other positive diagnostic criteria:			
Contact with known TB patient		109/176 (62%)	84/180 (47%)
CT-scan positive		121/141 (79%)	35/42 (80%)
Hydrocephalus		89/113 (79%)	42
Tuberculoma		10	7
Chest X-ray positive for TB		107/197 (54%)	243/479 (51%)
Miliary pattern		17	48
Mantoux >10mm		17/176 (66%)	90/180 (50%)
Results		6 months treatment	More than 6 months

		treatment
During treatment		
Number of failures	-	2
Non-compliant	4	66
Side-effects	1	1
Died	32/197 (16%)	41/675 (6%)
Treatment completed	160/197 (81%)	577/675 (85%)
Cured	120/160 (75%)	91/148 (61%)
Residual neurological deficits	40/160 (25%)	57/148 (39%)
During follow-up		
Duration of follow-up	Mean 15 mths (range 4-33) 85% at least 12 mths	Mean 15 mths (range 4-36) 92% at least 12 mths
On completion of follow-up, absolute numbers and rates for patients		
Who completed treatment	131 (82%)	591 (≥85%)
Relapse	2	0
Died	2	24
Cured	33/39 (85%)	188/307 (61%)
Residual neurological deficits	6/39 (15%)	119/307 (39%)
	<ul style="list-style-type: none"> • The authors found that relapse occurred in 2/131 (1.5%) of the group with treatment duration of 6 months and in 0 out of 591 patients who received longer than 6 months treatment. (NB data on relapse rates only available for 82% of those in the 6-month treatment group and for 88% of those in the more than 6-months group). • In the 6 months duration group treatment was completed by 127/147 (86%) of the children and by 33/50 (66%) of the adults, while in the more than 6 months duration group the completion rates were very similar, at 447/515 (87%) and 130/160 (81%) respectively. • Mortality in the children in the 6 months treatment group was lower than in adults (14% and 24% respectively). In the more than 6 months group, mortality was 11% in the children and 2% in the adults. • In the less than 6 months group 93/127 (73%) of the children were cured, while 34/127 (27%) were cured but had neurological deficits. In the adults, these rates were 27/33 (82%) and 6/33 (18%) respectively. In the more than 6 months group not all studies reported this information however it was calculated that 32/68 (47%) of the children were cured and 36/68 (53%) were 	

	cured but had neurological deficits. In the adults these rates were 59/80 (73%) and 21/80 (27%) respectively.
SIGN quality rating	-
Evidence hierarchy grading	3
Comments	<ul style="list-style-type: none"> • A large number of patients (501) in the more than 6-months treatment group were excluded from the analysis because there was insufficient information. • A 6-month treatment regimen has never been compared to longer treatment in one study thus the comparison here is between case series studies of different durations. • Studies were not quality appraised. • The studies were combined to calculate percentages however the denominators show that in terms of many outcomes, data was incomplete (e.g. cure rates in the more than 6-months group). • The authors concluded that “although no studies have compared 6 month treatment regimens with longer treatment, it can be concluded that 6 months treatment is sufficient for tuberculous meningitis with fully susceptible mycobacteria”. This conclusion does not necessarily flow from the evidence reviewed as a large number of patients were excluded from the analysis, the groups were not the same at baseline, the studies which were included were not quality appraised, there may be differences in the way diagnosis and neurological deficits were assessed across the studies and in some studies patients were additionally on steroids. Furthermore, the mortality reported was higher in the 6-months duration group than in the longer than 6-months duration group. • NB this study has been included to address the issue of duration of treatment for children with TB meningitis, as children represent approximately 75% of the patients included in this review.
NCC CC ID	9

Evidence Table	
MGTM1b: In children with TB meningitis disease, is a standard drug treatment regimen of less than twelve months, as effective as a twelve month drug treatment regimen in eradicating TB?	
Author / title / reference / yr	Ramachandran, P., Duraipandian, M., Nagarajan, M., Prabhakar, R., Ramakrishnan, C. V., & Tripathy, S. P. 1986, "Three chemotherapy studies of tuberculous meningitis in children", <i>Tubercle.</i> , vol. 67, no. 1, pp. 17-29
N=	N=103 patients in two study arms (Regimens II and III). One of the three study arms (N=77) did not contain pyrazinamide (Regimen I). Setting: Institute of Child Health and Hospital for children, Madras.
Research design	Case series
Aim	To undertake three consecutive studies to evolve suitable regimens for the treatment of TB meningitis in children.
Population	Patients with TB meningitis, aged between 1 and 12 years who had received not more than 4 weeks of anti-tuberculosis treatment and had no evidence of renal or liver disease. Diagnosis was based on clinical symptoms and signs, notably fever, vomiting, irritability, apathy, refusal to play, anorexia, constipation, well-marked meningeal signs, impaired consciousness, coma and widespread paralysis. The cerebrospinal fluid (CSF) findings were also taken into consideration.
Intervention	All regimens were for 12 months. N= 29. Regimen II: Streptomycin plus isoniazid plus rifampicin plus pyrazinamide daily for the first 2 months, followed by ethambutol plus isoniazid daily for 10 months. N=74. Regimen III: Streptomycin plus isoniazid plus pyrazinamide daily and rifampicin twice a week for the first 2 months, followed by ethambutol plus isoniazid daily for 10 months. The streptomycin dosage was 40mg/kg body-weight, rifampicin 12mg/kg, ethambutol 17.5mg/kg and pyrazinamide 30mg/kg. Corticosteroids were administered to all the patients for a period of 6-12 weeks. Seriously ill patients (stages II and III) were given dexamethasone by the intramuscular route in a dosage of 2-4mg every 6-8 hours for the first 3 or 4 days followed by oral prednisolone (1-2mg/kg). Patients clinically diagnosed to have developed hydrocephalus were investigated, and surgery (ventriculo-peritoneal shunt) was performed, if indicated.
Comparison	No treatment duration comparison.
Outcome	Number of deaths, relapse, neurological sequelae, complete recovery and incidence of jaundice are

	<p>all reported separately for each treatment regimen.</p> <p>Neurological sequelae was classified as follows: Mild residual damage implied such sequelae as hyperactivity, irritability, mild perceptual defects and limited motor impairment such as facial paresis or monoparesis. Moderate residual damage included such defects as hemiparesis, involuntary movements and substantial mental impairment. Patients with severe residual damage usually remained unconscious and even if consciousness was regained, they were incapable of independent existence.</p>
Characteristics	<p>Characteristics are only presented for the entire study (N=180), not for the three regimens separately.</p> <p>A tuberculin skin test yielded an induration of 10mm or more in 50% of patients. In all, 84 (47%) of patients had a history of contact with a known case of pulmonary TB and 9 (5%) had an abnormal chest radiograph suggestive of pulmonary TB. A CSF protein value of more than 40mg/100ml on admission was observed in 96% of patients. CSF smear results for acid fast bacilli were available for the 103 patients in regimens II and III only. Of these, in 25 (23%) smear alone was positive, in 12 (12%) both smear and culture were positive and in 24 (23%) culture alone was positive.</p> <p>The nutritional status of the patients was very poor. Using growth standards set up by the Indian Council of Medical Research, only 2% of patients were considered normal, while 64% had mild to moderate malnutrition and 34% severe malnutrition based on deficit in weight for age.</p> <p>Age distribution: 53% of patients were aged less than 3 years Only 17% were aged 5 years or more.</p> <p>Stage of disease on admission: Stage 1: N=24 (13%) Stage 2: N=139 (77%) Stage 3: N= 17 (9%)</p> <p>(The stage classifications used were a modification of those used by the British Medical Research Council and are described as follows: 1) Stage I: Patients were conscious and had mainly non-specific symptoms, with or without signs of meningeal irritation, but no focal neurological signs. Diagnosis was established mainly on CSF findings; 2) Stage II: Patients were mentally confused and/or had neurological signs and 3) Stage III: Patients were comatose and had gross neurological signs).</p>

Results	<ul style="list-style-type: none"> • N=94 (91%) patients were analysed in Regimens II and III. (This omits patients discharged against medical advice before completing treatment). • There were 26 deaths (28%) in Regimens II and III at 12 months due to TB meningitis. • There were 36 patients (38%) suffering from residual damage at 12 months in Regimens II and III. Of these patients, 7 had mild damage, 25 had moderate damage and 4 had severe damage. • A full recovery was made by 32 patients (34%) in Regimens II and III. • The incidence of jaundice in the first 2 months was 21% in Regimen II and 5% in Regimen III. • Several complications were reported (e.g. hydrocephalus, blindness and optic disk changes) but not separately for each regimen. • There were no relapses at 24 months follow-up.
SIGN quality rating	No level 3 critical appraisal checklist available.
Evidence hierarchy grading	3
Comments	<ul style="list-style-type: none"> • Baseline characteristics for each of the regimens are not reported separately. • It is unclear how the cause of death was assessed to be TB-related. • The poor nutritional state of the patients means it is difficult to generalise the study to the UK. • The authors note “there were no relapses during the follow-up period, indicating that regular therapy for 12 months is adequate for the treatment of TB meningitis”. It is not clear however, how many deaths and changes in neurological sequelae status were found when status was assessed at 24 months in each treatment regimen.
NCC CC ID	205

Evidence Table	
MGTM1b: In children with TB meningitis disease, is a standard drug treatment regimen of less than twelve months, as effective as a twelve month drug treatment regimen in eradicating TB?	
Author / title / reference / yr	Jacobs, R. F., Sunakorn, P., Chotpitayasunonah, T., Pope, S., & Kelleher, K. 1992, "Intensive short course chemotherapy for tuberculous meningitis", <i>Pediatric Infectious Disease Journal.</i> , vol. 11, no. 3, pp. 194-198.
N=	N=45 Eight other children were included in this study, (4 each in two other study arms) however these were 9 and 12 month regimens which did not included pyrazinamide. Setting: Bangkok Children's Hospital, Thailand.
Research design	Case series (as only one treatment arm of interest).
Aim	To compare the outcomes of three different treatment durations and combinations of treatment in children with TB meningitis (although only one considered here).
Population	Children diagnosed with TB meningitis between 1986 and 1990. The criteria for diagnosis was characteristic cerebrospinal fluid (CSF) findings of pleocytosis with mononuclear predominance, decrease in glucose content initially or during the course of the disease, elevated protein content and two or more of the following: a positive tuberculin skin test, ≥ 10 mm induration, radiographic evidence of pulmonary TB that included parenchymal or hilar lymph node involvement, history of contact with a known TB patient or presence of <i>M tuberculosis</i> in CSF.
Intervention	A 6 month regimen of therapy consisting of isoniazid, rifampicin, pyrazinamide and streptomycin for 2 months and isoniazid and rifampicin for 4 months. Daily doses were: isoniazid 15mg/kg, rifampicin 20mg/kg, pyrazinamide 30mg/kg and streptomycin 40mg/kg. A glucocorticoid was routinely administered as dexamethasone, 0.3 to 0.5mg/kg/day, in the first week of treatment followed by prednisolone, 2mg/kg/day, for 3 to 4 weeks with tapering dosages for all children with Stage II and Stage III disease. Children who had elevated pressure (>200 mm H ₂ O) and whose condition was severe or progressed rapidly during hospitalisation had ventriculostomies placed for periods of 2 to 3 days. Those children with obstructive or persistent hydrocephalus had ventriculoperitoneal shunts inserted and hydrocephalus was declared as sequelae.
Comparison	No comparison as other arms did not contain pyrazinamide.
Outcome	The study outcomes were mortality and sequelae and were combined to represent total negative outcomes. The neurologic sequelae identified in the study included hydrocephalus, cerebral palsy

	with mental retardation, hemiparesis, long term seizures and behavioural changes.
Characteristics	<p>In all of the study patients (including the 8 patients in the 2 other arms) the baseline characteristics were: N=26 (49.1%) male and 27 (50.9%) female. Age 0-6 months, N=8 (15.1%) 7 to 24 months, N=21 (39.6%) 2 to 5 years, N=7 (13.2%) over 5 years, N=17 (32.1%).</p> <p>In terms of criteria for diagnosis, 85% had a positive history of contact, 66% a positive chest roentgenogram, 47% a positive intracutaneous tuberculin skin test, 14.3% (5/35) a positive CSF culture, 6.1% (2/33) a positive CSF acid-fast stain and a BCG scar was found in 52.8%. (NB age, sex and criteria for diagnosis were not reported separately for each study arm)</p> <p>Of the 45 patients on the 6 month therapy which included pyrazinamide: In Stage I, N=8 (17.8%) In Stage II, N=25 (55.6%) In Stage III, N=12 (26.7).</p> <p>(The stages are defined as 1) Stage I: clinical presentation of fever with meningeal signs; the only diagnostic clue is the characteristic CSF; 2) Stage II: findings in Stage I associated with signs of increased intracranial pressure, paresis of extremities or cranial nerve palsy; and 3) Stage III: findings in Stages I and II associated with severe impairment in consciousness and/ or decerebrate posturing).</p>
Results	<ul style="list-style-type: none"> • There were 7 (15.6%) deaths. Five of these deaths (71.4%) were within the first 3 days of hospitalisation. • Five (5/12, 41.6%) of the deaths were in Stage III patients and 2 (2/33, 6.1%) in Stage I or II patients. • In those surviving (N=38), 11 experienced sequelae (28.9%). Ten (10/31, 32.3%) of these patients were in Stage I or II and one (1/7, 14.3%) was in Stage III. • Total adverse outcomes (death plus sequelae) were found in 18 (40%) of patients. Of these, 12 (12/33, 36.4%) were in Stage I or II and 6 (6/12, 50%) were in Stage III. • At least one years follow-up was available on 27 of 38 survivors and less than 1 year follow-up on 7 of 38, 4 children had been lost to follow-up after 6 months. No relapses of TB meningitis were

	documented in any of these cases.
SIGN quality rating	No level 3 critical appraisal checklist available.
Evidence hierarchy grading	3
Comments	<ul style="list-style-type: none"> • An upper age limit for children in the study is not given so it is unclear how “child” was defined. • How neurological sequelae were assessed is not specified and types of sequelae are not specified for the surviving patients on this treatment regimen. • Cause of death is not reported. • The authors note that economic factors restrained the use of pyrazinamide for a 9 or 12 month duration regimen. They concluded that pyrazinamide should be included as standard therapy in all cases of TB meningitis, regardless of the duration of treatment.
NCC CC ID	199

Evidence Table

MGTM1b: In children with TB meningitis disease, is a standard drug treatment regimen of less than twelve months, as effective as a twelve month drug treatment regimen in eradicating TB?	
Author / title / reference / yr	Goel, A., Pandya, S. K., & Satoskar, A. R. 1990, "Whither short-course chemotherapy for tuberculous meningitis?", <i>Neurosurgery.</i> , vol. 27, no. 3, pp. 418-421.
N=	N=35 Setting: Neurosurgery outpatient department, Seth GS Medical College and KEM hospital, Bombay, India.
Research design	Case series
Aim	To report a series of patients who had tuberculosis in the brain and had discontinued treatment before the end of the recommended 2-year period.
Population	Between 1980 and 1987, 781 patients were diagnosed with TB meningitis. Examination of the cerebrospinal fluid (CSF) showed lymphocytic meningitis with raised protein levels and low glucose levels. All patients were advised to maintain antituberculous therapy for 2 years. Fifty-seven patients died during their hospital stay. Of the 724 patients discharged, 236 were available for regular follow-up and were cured at the end of 2 years of therapy with no reoccurrence during follow-up. Thirty-seven patients stopped antituberculosis treatment prematurely against advice. Of these, 35 were readmitted with recurrent TB meningitis. Of the 2 who stopped drug treatment early but had no recurrence, one had been treated for 8 months and the other for 10 months. The remainder of the patients' (451) were not available for follow-up after discharge from the hospital. The 35 patients readmitted for recurrence are reported in this study.
Intervention	Streptomycin 1g/d (appropriate dose for children) x 90 Pyrazinamide: 20mg/kg/d for 3 months Rifampicin 10mg/kg/d for 9 months Isoniazid 5mg/kg/d for 2 years Ethambutol 15mg/kg/d for 2 years Pyridoxine 10-40mg/d
Comparison	Limited comparison with patients who completed 2 years of treatment.
Outcome	Duration of drug therapy in relapsing patients, signs and symptoms and death.
Characteristics	Sex: 20 (57%) male and 15 (43%) female.

	<p>Severity of initial illness on admission graded using the system developed by Gordon and Parsons: Grade I: 20% Grade II: 62.8% Grade III:17.1% Age: ≤15 years, N=25 (71%) ≥16 years, N=10 (29%) (The 236 patients who completed treatment had very similar severity gradings but were slightly younger (≤15 years, 79% and ≥16 years, 21%)).</p>
Results	<ul style="list-style-type: none"> • The duration of drug therapy in the 35 patients who showed recurrence was: < 6 months, N= 20 (57%) 6 to <12 months, N=8 (23%) 12 to 24 months, N=5 (14%) Irregular treatment, N=2 (6%) • Ten patients were critically ill. Five patients had bilateral decerebration, 10 had hemiparesis and 10 had optic atrophy. Eight patients were diagnosed as having tuberculomas and the rest had TB meningitis with different degrees of hydrocephalus diagnosed on the basis of computed tomography, angiography and ventriculography. • Nine patients with evidence of raised intracranial pressure underwent CSF diversion with shunts and 2 underwent surgery for tuberculoma. • N=13 (37.1%) died during their hospital stay.
SIGN quality rating	No level 3 critical appraisal checklist available.
Evidence hierarchy grading	3
Comments	<ul style="list-style-type: none"> • Limited diagnostic assessments were performed / reported. • No reporting of use of corticosteroids. • It is notable that the majority of relapsing patients (57%) took treatment for less than 6 months, which has never been advocated as suitable treatment duration for TB meningitis. • A large number of patients (451 or 62 %) were lost to follow-up and thus their outcomes in terms of relapse and duration of treatment taken are not known. Unless patients had left the area it is unlikely that they would not have returned to the hospital if they developed recurrence, however there is no way of knowing how many discontinued therapy before 2 years. • The authors conclude “patients with TB meningitis treated for 2 years with chemotherapy showed no recurrence during the follow-up as compared with patients who were treated inadequately for a

	<p>period of less than 2 years. It is recommended that, until adequate proof is available regarding the adequacy of short-term chemotherapy, patients should be treated for a period of 2 years”.</p> <ul style="list-style-type: none">• NB This study includes both adults and children however children represent the largest proportion of the total patients included (71%).
NCC CC ID	203

Evidence Table	
MGTM1b: In children with TB meningitis disease, is a standard drug treatment regimen of less than twelve months, as effective as a twelve month drug treatment regimen in eradicating TB?	
Author / title / reference / yr	Donald, P. R., Schoeman, J. F., Van Zyl, L. E., De Villiers, J. N., Pretorius, M., & Springer, P. 1998, "Intensive short course chemotherapy in the management of tuberculous meningitis", <i>International Journal of Tuberculosis & Lung Disease.</i> , vol. 2, no. 9, pp. 704-711.
N=	N=95 Setting: Department of Paediatrics and Child Health, Tyerberg Hospital (tertiary care), South Africa.
Research design	Case series
Aim	To describe the experience of treating 95 children with complicated TB meningitis with intensive short course chemotherapy of 6 months duration.
Population	A consecutive series of children admitted with TB meningitis. Diagnosis was by cerebrospinal fluid (CSF) findings (cell count, protein and glucose concentration), <i>M. tuberculosis</i> culture from CSF or gastric aspirate, tuberculin test, computerised tomography (CT) scan, chest radiography or a history of close household contact with an adult with pulmonary tuberculosis.
Intervention	Isoniazid (20mg/kg), rifampicin 20mg/kg, pyrazinamide 40mg/kg and ethionamide 20mg/kg, all given in a single daily dosage. Dosages were increased appropriately as the children gained in weight. Forty of the children also received prednisolone as part of a randomised trial. In addition, they received daily acetazolamide and furosemide during the first month of treatment to expediate normalisation of intra-cranial pressure.
Comparison	No comparison
Outcome	Number of deaths, motor defects, relapse rate and hepatotoxicity (assessed by total bilirubin).
Characteristics	Using British Medical Research Council Criteria: N=4 (4%) at stage I with a median age of 37 months. N=52 (55%) at stage II with a median age of 38 months. N= 39 (41%) at stage III with a median age of 17 months. (Those at stage I disease are fully conscious and have no pareses, those at stage II are stuporous and may have focal neurological signs or hemiparesis, and those at stage III are comatose or have a complete hemiplegia or quadriplegia). Diagnostic criteria: In 90 (95%) a total CSF cell count of $<500 \times 10^9/l$ was obtained on the initial diagnostic lumbar

	<p>puncture. A total CSF protein of $\geq 0.8\text{g/l}$ was found in 84 children (88%) and a glucose concentration of $< 2.2\text{mmol/l}$ in 67 children (70%).</p> <p>In 18 children (19%) a culture of <i>M tuberculosis</i> from the CSF confirmed diagnosis while in 31 (33%) there was culture from gastric aspirate. Eighty-four children (88%) had a tuberculin test induration of $> 10\text{mm}$ and 41 (43%) had chest radiography indicative of TB. Fifty-five (58%) had a history of recent close household contact with an adult with pulmonary TB. Only one child was diagnosed on the basis of clinical features and CSF findings only.</p> <p>On CT scan: Hydrocephalus, N=82 (86%) Basal exudate, N=63 (66%) Tuberculomata, N=6 (6%) Infarction, N=22 (23%)</p> <p>A non-communicating hydrocephalus was present in 21 children (22%) all of whom were referred for an immediate peritoneal shunt. In a further 6 patients (6%) an unsatisfactory response to medical management also led to a ventriculo-peritoneal shunt being performed during the first month of treatment.</p>
Results	<ul style="list-style-type: none"> • Ten (26%) of stage III patients and 3 (6%) at stage II died before completion of therapy. • Of the 29 stage III children who survived at completion of 6 months treatment, 12 (41%) had one or more major motor defects, while of the 49 stage II survivors, 10 (20%) had a major motor deficit. • Thus in total, 13 patients (14%) died before completion of treatment and of the survivors, 22 (27%) had motor deficits. • Among the 82 (91%) patients who completed 6 months of treatment, 5 moved immediately after discharge and could not be traced, 7 moved during follow-up and could not be traced, 2 died (thus overall mortality was 16% excluding any deaths in those lost to follow-up) and 3 were inadvertently re-started on chemotherapy. One child experienced a probable recrudescence within one month of stopping chemotherapy. • Eighteen children (20%) developed a mildly elevated serum bilirubin concentration during the first month of treatment. In 5 of these children, treatment was stopped and streptomycin and ethambutol substituted. In all instances the original treatment could be introduced without any complications upon normalisation of liver function, which usually occurred within 2-3 weeks.
SIGN quality rating	No level 3 critical appraisal checklist available.
Evidence hierarchy grading	3
Comments	<ul style="list-style-type: none"> • The authors state that they are reasonably certain despite lack of post-mortem evidence that the

	<p>two children, who died during follow-up, died from complications due to severe neurological damage rather than recrudescence of disease.</p> <ul style="list-style-type: none"> • It is not explicit how “major motor deficits” were assessed. • Thirteen (16%) of the children who completed treatment were subsequently lost to follow-up so the occurrence of relapse in this group is not known. • Details are not explicitly reported for the 4 stage I patients. • The authors conclude that “our experience of intensive short course chemotherapy in a relatively large number of very young children with advanced, complicated forms of TB meningitis, illustrates that the great majority of children can be safely treated for 6 months with high doses of anti-tuberculosis agents with a very low relapse rate during the first year after stopping therapy”.
NCC CC ID	197

Evidence Table

MGTM2: In patients of all ages with TB meningitis disease, do corticosteroids as an adjunct to an anti-tuberculosis drug treatment regimen, decrease morbidity and mortality compared to an anti-tuberculosis drug regimen alone?	
Author / title / reference / yr	Prasad K, Volmink J, Menon GR. Steroids for treating tuberculous meningitis (Cochrane Review). In: The Cochrane Library, Issue 1, 2004. Chichester, UK: John Wiley & Sons, Ltd
N=	N=595 patients from 6 studies (searches updated to March 2003) Studies included: Chotmongkol 1996 (N=59, Thailand), Girgis 1991 (N=280, Egypt), Kumarvelu 1994 (N=41, India), Larizabal 1998 (N=58, the Phillipines), O'Toole 1969 (N=23, India), Schoeman 1997 (N=134, South Africa). Studies excluded (reason for exclusion): Escobar 1975 (not an RCT), Frieman 1970 (trial of intrathecal hydrocortisone), Girgis 1983 (not an RCT), Hockaday 1966 (not an RCT), Kapur 1969 (not an RCT), Lepper 1963 (alternate allocation in the first half of the study), Voljavec (not an RCT), Wasz-Hockert 1963 (trial with historical control), Weiss 1965 (not an RCT). Duration: Follow-up 3 mths to 2 years.
Research design	Systematic review and meta analysis
Aim	To assess the effects of steroids on death and disability in patients with tuberculous meningitis (TBM).
Population	Patients with clinically diagnosed TBM regardless of age, gender or HIV status.
Intervention	N=301. Any steroid (hydrocortisone, prednisone, prednisolone or dexamethasone) given by the oral, intramuscular or intravenous route in combination with anti-TB medication. No specified dose. The corticosteroid used in different studies were: dexamethasone (O'Toole 1969, Girgis 1991, Kumarvelu 1994, Lardizabal 1998) and prednisolone (Chotmongkol 1996, Schoeman 1997).
Comparison	N= 294. The control groups were on anti-TB medication only.
Outcome	Primary outcomes: Death or death or disabling deficit ant the end of follow up. Other outcomes: Adverse effects: upper gastrointestinal bleeding, invasive bacterial or fungal infections, hyperglycaemia, psychosis or any other adverse effect.
Characteristics	Trials assessed the effects of steroids in young children (Schoeman 1997), adults (Lardizabal 1998, Chotmongkol 1996, Kumarvelu 1994), or both (O'Toole 1969, Girgis 1991). Two studies Schoeman 1997, Lardizabal 1998) included only patients with stage II and III disease while the rest included

	patients with all stages of severity.
Results	<ul style="list-style-type: none"> • Steroids were associated with fewer deaths (RR= 0.79; 95%CI 0.65-0.97) and a reduced incidence of death and severe residual disability (RR= 0.58; 95%CI 0.38-0.88). • Subgroup analysis suggests an effect on mortality in children (RR= 0.77; 95%CI 0.62-0.96) but the results in a smaller number of adults are inconclusive (RR= 0.96; 95%CI 0.5-1.84) . • For death as the outcome of interest the effects of steroids were similar among patients with mild to moderate disease (RR= 0.66, 95% CI 0.41 to 1.06) and those with severe disease (RR=0.81; 95%CI 0.66 to 0.99). (Severity was measured by the British Medical Research Council staging system). There is thus little evidence that the severity of disease influences the effects of steroids on mortality. The value of steroids in the least severe category (stage 1) could not be determined in this review. • Adverse effects were reported in only four small trials (Chotmongkol 1996, Kumarvelu 1994, O'Toole 1969 and Lardizabal 1998), and in these cusingoid features appear to be the most common. • In two studies (Kumarvelu 1994, Schoeman 1997) loss to follow-up occurred. The robustness of the findings was tested by performing an intention-to-treat analysis using the worst case scenario i.e. assuming that all those lost to follow up in the experimental group experienced adverse outcomes while those lost in the control group had favourable outcomes. The results became marginally non-significant both for death (RR 0.85, 95% CI 0.7 to 1.03) and for death or disabling residual deficit (0.75, 95%CI 0.51 to 1.10).
SIGN quality rating	++
Evidence hierarchy grading	1++
Comments	<ul style="list-style-type: none"> • Only RCTs included (quasi-randomised studies excluded). • Allocation concealment was not reported in any of the trials, thus the chance of selection bias cannot be ruled out as a possible explanation for the results found. • Funnel plots showed marked asymmetry in keeping with publication bias. • Heterogeneity was detected among trials assessing the effect of steroids in patients with severe (stage III) disease (chi-squared 8.25 (df=4); p=0.08). • No evidence is available to support the use of steroids in HIV positive patients with TBM. • Authors conclusions: "Evidence from published trials suggest steroid use for treating TBM is associated with a reduced incidence of death and/or disability. However, some caution is warranted as studies are small and publication bias is likely".
NCC CC ID	24

Evidence Table	
MGTM2: In patients of all ages with TB meningitis disease, do corticosteroids as an adjunct to an anti-tuberculosis drug treatment regimen, decrease morbidity and mortality compared to an anti-tuberculosis drug regimen alone?	
Author / title / reference / yr	Dooley, D. P., Carpenter, J. L., & Rademacher, S. 1997, "Adjunctive corticosteroid therapy for tuberculosis: A critical reappraisal of the literature", <i>Clinical Infectious Diseases</i> , vol. 25, no. 4, pp. 872-887.
N=	N=7 studies which had to have a study group (using adjunctive corticosteroid therapy) and a control group (no corticosteroid therapy). Studies included: Ashby 1955 (N=12), Voljavec 1959 (N=33), Lepper 1963 (N=37), O'Toole 1969 (N=23), Escobar 1975 (N=72), Girgis 1983 (N=136) and Girgis 1991 (N=160).
Research design	Systematic review
Aim	To critically review the published literature addressing corticosteroid usage in therapy for TB (including a section on TB meningitis).
Population	Patients with TB meningitis (although not all patients were definitively proven to have TB meningitis on the basis of a positive culture or a stain of a tissue biopsy).
Intervention	A defined course of adjunctive corticosteroid therapy.
Comparison	Anti-tuberculosis medication only.
Outcome	Death, sequelae, time to negativity of sputum culture.
Characteristics	Variable across studies.
Results	<ul style="list-style-type: none"> • Five of these 7 trial demonstrated an advantage of adjunctive corticosteroid therapy over standard therapy for survival, frequency of sequelae, or both. • Studies that stratified illness by severity at presentation (Voljavec 1959 and Girgis 1991) noted the lack of effect of corticosteroids on either early disease or late disease (coma) but a significant benefit for patients with intermediate disease. • Three studies with shorter corticosteroid regimens of 2-4 weeks (Lepper 1963, O'Toole 1969 and Girgis 1983) demonstrated disappointing results; those studies with longer regimens of 4 weeks to "months" (Ashby 1955, Voljavec 1959, Girgis 1991 and Escobar 1975) demonstrated significant beneficial effects. • A regimen of dexamethasone at 8-12mg/d (Girgis 1991 and Girgis 1983), or a prednisone equivalent (Escobar 1975) seemed as effective as, and had fewer side effects than higher doses (Escobar 1975).

SIGN quality rating	-
Evidence hierarchy grading	2-
Comments	<ul style="list-style-type: none"> • Some elements of quality are considered but not systematically and studies were not excluded on the basis of quality. Of the 7 trials included only two are RCTs so for the others potential confounding factors have not been considered. • Some of the studies described as being randomised (e.g. Escobar 1975 and Girgis 1983) did not appear to be randomised when the original studies were checked. • The authors assert that five of these seven trials demonstrated an advantage of adjunctive corticosteroid therapy over standard therapy in terms of survival, frequency of sequelae or both. However, many of the studies are small and it should be clarified that in terms of survival, only one RCT showed a statistically significant difference in terms of mortality (Girgis 1991).
NCC CC ID	275

Evidence Table	
MGT2: In patients of all ages with TB meningitis disease, do corticosteroids as an adjunct to an anti-tuberculosis drug treatment regimen, decrease morbidity and mortality compared to an anti-tuberculosis drug regimen alone?	
Bibliographic reference	Thwaites, G. E., Nguyen, H. D., Hoang, T. Q., Do, T. T., & Nguyen, T. C. 2004, "Dexamethasone for the treatment of tuberculous meningitis in adolescents and adults", <i>New England Journal of Medicine</i> , vol. 351, no. 17, pp. 1741-1751.
Study type	RCT
Evidence level	1++
Study objective	To determine whether adjunctive dexamethasone therapy improves the outcome in patients over 14 years of age who have TB meningitis with or without HIV infection.
Number of patients	N=545 (618 assessed for eligibility) Setting: Two centres in Ho Chi Minh City, Vietnam. The two 500 bed hospitals serve the local community and act as tertiary referral centres.
Patient characteristics	<p>Only patients over 14 years of age with clinical evidence of meningitis (defined as the combination of nuchal rigidity and cerebrospinal fluid abnormalities) were eligible to enter the study. TB meningitis was defined as "definite" if acid-fast bacilli were seen in the cerebrospinal fluid. It was defined as "probable" in patients with one or more of the following: suspected active pulmonary TB on chest radiography, acid-fast bacilli found in any specimen other than the cerebrospinal fluid and clinical evidence of other extrapulmonary TB. TB meningitis was defined as "possible" in patients with at least four of the following: a history of TB, predominance of lymphocytes in the cerebrospinal fluid, a duration of illness of more than five days, glucose to plasma glucose of less than 0.5, altered consciousness, yellow cerebrospinal fluid or focal neurologic signs.</p> <p>Patients were reclassified on discharge as having definite TB meningitis if acid-fast bacilli were seen or <i>M tuberculosis</i> was cultured from the cerebrospinal fluid, or as not having TB meningitis if another diagnosis was confirmed by microbiologic or histopathological evaluation. Patients were not eligible to enter the trial if the enrolling physician believed that corticosteroids were contraindicated, if the patient had received more than one dose of any corticosteroid or more than 30 days of antituberculous treatment immediately before study entry, or if the consent of either the patient or the patient's relatives was not obtained.</p> <p><i>M tuberculosis</i> was cultured from the cerebrospinal fluid or another site in 170 patients (31%), 85 from each group. Of these, 58% were susceptible to all first line drugs, 35% were resistant to streptomycin,</p>

	<p>isoniazid or both, 1 was monoresistant to rifampicin and 6% were resistant to at least isoniazid and rifampicin.</p> <p>Median age was 35 years and 60% were male, median duration of symptoms was 15 days, median weight was 45kg, median score on the Glasgow coma scale was 14 (3 is worst and 15 is best with 13 or higher indicating only mild brain injury), 18% were HIV positive (only 4% of all participants were not HIV tested). Diagnosis at discharge was definite in 34%, probable in 48%, possible in 17% and not TB meningitis in 1%.</p> <p>MRC grade denotes British Medical Research Council Criteria. Grade I indicates a Glasgow coma score of 15 with no neurologic signs, grade II indicates a score of 11 to 14 (or 15 with focal neurologic signs) and grade III a score of 10 or less. In this study 32% were grade I, 45% were grade II and 22% were grade III.</p>
Intervention	<p>N=274 dexamethasone</p> <p>Adults previously untreated for TB received three months of daily oral isoniazid (5mg per kg of body weight), rifampicin (10mg per kg) pyrazinamide (25mg per kg; maximum 2g per day) and intramuscular streptomycin (20mg per kg; maximum 1g per day) followed by six months of isoniazid, rifampicin and pyrazinamide at the same daily doses. Ethambutol (20mg per kg maximum 1.2g per day) was substituted for streptomycin in the cases of HIV infected patients and was added to the regimen for three months for patients who had been treated previously for TB. Drugs were administered by nasogastric tube to patients who were unable to swallow. None of the patients received antiretroviral drugs.</p> <p>Patients were stratified on entry according to their MRC grade. Patients within each grade were randomly assigned to received dexamethasone sodium phosphate or placebo as soon as possible after the start of antituberculosis treatment. Patients with grade II or III disease received intravenous treatment for four weeks (0.4mg per kg per day for week 1, 0.3mg per kg per day for week 2, 0.2mg per kg per day for week 3 and 0.1mg per kg per day for week 4) and then oral treatment for four weeks, starting at a total of 4mg per day and decreasing by 1mg each week. Prolonged intravenous dexamethasone treatment of patients with mild disease was not considered acceptable. Therefore patients with grade I disease received two weeks of intravenous therapy (0.3mg per kg per day for week 1 and 0.2 mg per kg per day for week 2) and then four weeks of oral therapy (0.1mg kg per day for week 3 then a total of 3mg per day, decreasing by 1mg each week).</p>
Comparison	N=271 Placebo (identical in appearance to dexamethasone)
Length of follow-up	9 months
Outcome measures	Primary outcome:

	<p>Death or severe disability 9 months after randomisation. Disability was assessed using the Rankin scale. Simple questions categorized outcome in survivors by determining whether they required help with everyday activities such as eating, washing and going to the toilet. If the patients answered yes they were regarded as severely disabled. Patients were also tested on “dependence” on the Rankin scale (0-5) where 0 indicated no symptoms and 5 indicated total dependence on others, needing help day and night. Those who scored 3-5 were classified as having severe disability. At assessments, the worst score on either questionnaire was taken as the outcome. Two experienced Vietnamese physicians at each site were trained to assess disability with the Rankin scale.</p> <p>Secondary outcomes:</p> <p>Coma clearance time (days from randomisation until observations of a Glasgow coma score of 15 for more than 2 consecutive days).</p> <p>Fever clearance time (days from randomisation until observation of a maximal daily temperature of less than 37.5C for more than five consecutive days).</p> <p>Time to discharge from the hospital</p> <p>Time to relapse (defined by the onset of new focal neurological 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 randomisation)</p>
Effect size	<ul style="list-style-type: none"> • Treatment with dexamethasone was associated with a reduced risk of death (RR=0.69; 95%CI 0.52 to 0.92; P=0.01). It was not associated with a significant reduction in the proportion of severely disabled patients (34 of 187 patients [18.2%] among survivors in the dexamethasone group vs. 22 of 159 patients [13.8%] in the placebo group, P=0.27) or in the proportion of patients who had either died or were severely disabled after nine months (OR=0.81; 95%CI 0.58 to 1.13; P=0.22). • The treatment effect was consistent across subgroups that were defined by disease severity grade (stratified relative risk of death, 0.68; 95%CI 0.52 to 0.91; P=0.007) and by HIV status (stratified relative risk of death 0.78; 95%CI 0.59 to 1.04; P=0.08). • The time to fever clearance was significantly shorter in the dexamethasone group than in the placebo group (median, 9 vs. 11 days; P=0.03) but there was no significant difference between the dexamethasone and placebo groups in the time to coma clearance (median 9 vs 11 days; respectively P=0.23) or the time to hospital discharge (median 44 vs 54 days; P=0.57). • Relapse occurred in 89 patients (16.3%). 41 (15%) in the dexamethasone group and 48 (17.7%) in the placebo group (P=0.42) with no significant difference in time to relapse between the groups (median 41 days in the dexamethasone group vs. 38 days in the placebo group)

	<p>P=0.12).</p> <ul style="list-style-type: none"> Significantly fewer serious adverse events occurred in the dexamethasone group than in the placebo group (26 of 274 patients vs. 45 of 271 patients, P=0.02). In particular eight severe cases of hepatitis (one fatal) occurred in the placebo group and none occurred in the dexamethasone group (P=0.004).
Source of funding	Supported by the Wellcome Trust.
Additional comments	<ul style="list-style-type: none"> The authors concluded that adjunctive treatment with dexamethasone improves survival in patients over 14 years of age with TB meningitis regardless of disease severity, but probably does not prevent severe disability. The authors note that “the 98 HIV infected patients recruited to the trial were severely immunocompromised and none were treated with antiretroviral drugs. The treatment effect of dexamethasone was homogeneous across HIV subsets, and stratified subgroup analysis showed that dexamethasone was associated with a reduction in the risk of death that was not significant. The numbers of HIV infected patients were too small to confirm or reject confidently a treatment effect and the results may not be generalisable to populations with access to antiretroviral drugs. These data suggest however that dexamethasone is safe and may be of benefit in this group of patients”.
Citation	
NCC CC ID (Ref Man)	19998

Evidence Table	
MGTO 1: In patients with peripheral lymph node TB on drug treatment, are regimens of six months duration as effective as regimens of other durations in eradicating TB infection?	
Bibliographic reference	1992, "Six-months versus nine-months chemotherapy for tuberculosis of lymph nodes: preliminary results. British Thoracic Society Research Committee", <i>Respiratory Medicine</i> , vol. 86, no. 1, pp. 15-19. Campbell, I. A., Ormerod, L. P., Friend, J. A., Jenkins, P. A., & Prescott, R. J. 1993, "Six months versus nine months chemotherapy for tuberculosis of lymph nodes: final results", <i>Respiratory Medicine</i> , vol. 87, no. 8, pp. 621-623.
Study type	RCT
Evidence level	1+
Study objective	To test whether the use of pyrazinamide in the first 2 months would enable a 6 month regimen of rifampicin and isoniazid to be used in the treatment of lymph node TB instead of the (then) currently recommended 9 months.
Number of patients	N=199 Setting: UK hospitals
Patient characteristics	Patients aged 16-80 years with cervical, axillary or chest wall lymph node TB were eligible for the study provided they had never received chemotherapy for TB. Patients with active pulmonary parenchymal disease (but not isolated mediastinal lymphadenopathy) and those with significant hepatic renal or visual impairment or pregnancy were excluded from entry. On entry, patients were divided into one of three groups according to their management up to that point: those who had undergone surgical removal of all affected nodes (Group 1); those who had undergone biopsy or needle aspiration of nodes for diagnosis (Group 2) and those in whom the initial diagnosis was made clinically, supported by a positive tuberculin skin test (Group 3).
Intervention	N=63, E2H9R9, rifampicin and isoniazid for 9 months supplemented by 2 months initial ethambutol. N=70, Z2H9R9, rifampicin and isoniazid for 9 months supplemented by 2 months initial pyrazinamide. N=66, Z2H6R6, rifampicin and isoniazid for 6 months supplemented by 2 months initial pyrazinamide. The rifampicin dose was 450mg for patients under 50kg and 600mg for those 50kg and above. The pyrazinamide dose was 1.5mg for those under 50kg and 2.0mg for those 50kg and over. All patients received isoniazid 300mg daily. The ethambutol dose was 15mg/kg. All drugs were given once daily and the patients managed otherwise according to their physician's normal practice. Patients were not

	given corticosteroids.
Length of follow-up	30 months
Outcome measures	Treatment completed as planned. Treatment extended by clinician, modified or withdrawn Aspirations required. Speed of resolution of nodes. Percentage with residual nodes at the end of treatment Numbers developing fluctuation or sinuses. Relapse rates at 30 months.
Effect size	<ul style="list-style-type: none"> • There were 157 patients who completed the treatment as planned (79% E2H9R9, 80% Z2H9R9 and 77% Z2H6R6). A total of 14 (7%) were withdrawn before completing treatment (6 E2H9R9, 4 Z2H9R9 and 4 Z2H6R6) and a further 24 (12%) had their treatment modified (5 E2H9R9, 9 Z2H9R9 and 10 Z2H6R6). • The proportions of patients with remaining nodes at 6 months were 43% E2H9R9, 23% Z2H9R9 and 41% Z2H6R6 and at 9 months 28% E2H9R9 and 17% Z2H9R9 but differences were not statistically significant. • There were no statistically significant differences between the regimens in speed of resolution of nodes, or in the numbers developing fluctuation or sinuses. • Aspiration after commencement of treatment was performed in eight patients: seven on the E2H9R9 regimen and the other on Z2H6R6 (E2H9R9 versus al ZHR, P=0.005). • At 30 months 165 (83%) were followed up (78% E2H9R9, 83% Z2H9R9 and 88% Z2H6R6). Of those patients seen at 30 months, residual measurable nodes were reported in 6 (12%) of the E2H9R9, 10 (17%) of the Z2H9R9 and 10 (17%) of the Z2H6R6 groups. Nine patients were judged to have relapsed by their physicians and were retreated, 4 in the E2H9R9, 2 in the Z2H9R9 and 3 in the Z2H6R6 (one of whom had had an isoniazid resistant organism and had not received treatment as randomised). Before chemotherapy was restarted, tissue was sent for culture from five of these nine patients and none was positive. None of the above differences between the three treatment groups approaches significance and there were no significant differences in terms of enlargement of existing nodes (3 E2H9R9, 5 Z2H9R9 and 4 Z2H6R6), development of new glands (4 E2H9R9, 3 Z2H9R9 and 2 Z2H6R6) or sinuses (2 E2H9R9, 1 Z2H9R9 and 2 Z2H6R6) or the need for new operative procedures (2 E2H9R9, 1 Z2H9R9 and 2 Z2H6R6).
Source of funding	This trial was supported by Merrell Dow Pharmaceuticals.

Additional comments	<ul style="list-style-type: none"> • The study was not blinded. • There was no power analysis. • The authors conclude “the results at the end of therapy showed there was little difference between the regimens except in relation to aspiration after commencing chemotherapy: this was required in eight patients, seven on ethambutol and one on pyrazinamide, a difference which was significant (P=0.005). This may be because pyrazinamide is bactericidal and kills bacilli which are intracellular, making glands less likely to become fluctuant on treatment. The 6 months Z2H6R6 regimen performs just as well as the 9 month regimens Z2H9R9 and E2H9R9 in patients with fully sensitive organisms and has the additional benefits of convenience and reduced cost”.
NCC CC ID (Ref Man)	19750/1

Evidence Table	
MGTO1: In patients with peripheral lymph node TB on drug treatment, are regimens of six months duration as effective as regimens of other durations in eradicating TB infection?	
Bibliographic reference	Yuen, A. P., Wong, S. H., Tam, C. M., Chan, S. L., Wei, W. I., & Lau, S. K. 1997, "Prospective randomized study of thrice weekly six-month and nine-month chemotherapy for cervical tuberculous lymphadenopathy", <i>Otolaryngology - Head & Neck Surgery</i> , vol. 116, no. 2, pp. 189-192.
Study type	RCT
Evidence level	1-
Study objective	The aim of this study is to compare the efficacy of a thrice weekly 6 months regimen with a thrice weekly 9 month regimen in the treatment of cervical tuberculous lymphadenopathy.
Number of patients	N=113 recruited. N=5 defaulted treatment N=17 patients with drug reactions requiring modification of treatment. Thus 90 patients included in the analysis. Setting: Wanchai Chest Clinic of the Tuberculosis and Chest Service, Department of Health and the Otorhinolaryngology Clinic of the Department of Surgery, the Univerisy of Hong Kong, Hong, Kong.
Patient characteristics	All patients in this study had tuberculous lymphadenopathy affecting the cervical region only. Patients were not recruited if they were in relapse of previously treated cervical tuberculous lymphadenopathy or had prior antituberculous chemotherapy. All patients had fine needle aspiration of the lymph nodes for cytology and culture for Mycobacterium tuberculosis as the initial investigation for cervical lymphadenopathy. No attempt was made to excise all of the involved lymph nodes. Abscesses were drained surgically before the commencement of treatment. The female/male ratio was 1.4 in the 6 month regimen and 1.7 in the 9 month regimen. Mean age was 32 in the 6 month regimen and 28 in the 9 month regimen. Both groups had the same mean number of lymph nodes (3). The largest node size was mean 19mm in the 6 month regimen group and 23 in the 9 month group. In the 6 month regimen group 9% had abscesses and 5% had discharging sinus this was 2% for both in the 9 month regimen group. Bacterial cultures for the Mycobacterium tuberculosis were positive in 67 patients. Of the antibiotic susceptibility tests, 6 (9%) had strains resistant to streptomycin but treatment was not modified for

	these patients.
Intervention	N=43. The 6 month regimen was streptomycin (1gm intramuscular injection) isoniazid (15mg/kg), rifampicin (600mg) and pyrazinamide (2.5gm and 2gm for patients with body weight above and below 50kg respectively) 3 times a week for the first 4 months and then isoniazid (15mg/kg), rifampicin (600mg) for 2 months, 3 times a week. All patients received thrice weekly fully supervised treatment in the chest outpatient clinic.
Comparison	N=48. The 9 month regimen was streptomycin (1gm intramuscular injection) isoniazid (15mg/kg), rifampicin (600mg) and pyrazinamide (2.5gm and 2gm for patients with body weight above and below 50kg respectively) 3 times a week for the first 4 months and then isoniazid (15mg/kg), rifampicin (600mg) for 5 months, 3 times a week. All patients received thrice weekly fully supervised treatment in the chest outpatient clinic.
Length of follow-up	The median follow-up period after completion of treatment was 21 months, with the longest follow-up of 66 months.
Outcome measures	Primary failure was described as a persistent residual lymph node at the end of treatment confirmed to be persistent tuberculous lymphadenopathy by fine needle aspiration cytology or excision biopsy. A residual lymph node after completion of treatment was not considered failure of treatment as long as its size was decreasing or smaller than 0.5 cm diameter and it required no additional treatment. Relapse was defined as recurrence of a residual lymph node or appearance of a new node confirmed to be tuberculous lymphadenopathy after a period of initial clinical remission.
Effect size	<ul style="list-style-type: none"> • Of the 43 patients in the 6 months regimen, 2 (5%) had primary failure. Of the 48 patients in the 9 month regimen, 1 (2%) had primary failure. The 3% difference is statistically not significant (RR=2.23; 95%CI, 0.21 to 23.76). • Of those 88 patients who had initial clinical remission after completion of treatment, the 5 year actuarial remission rates of the two groups were 89% for the 41 patients receiving the 6 month regimen and 90% for the 9 month regimen. The 1% difference is statistically not significant (p=0.44).
Source of Funding	Supported in part by a research grant from the university of Hong Kong
Additional comments	<ul style="list-style-type: none"> • Randomisation processes and concealment are not described and the study is not blinded. • This is a relatively small study with no power analysis and thus it could be underpowered. • The study does not use an intention to treat analysis. • Streptomycin is not used as first line treatment for TB in the UK. Also the initial intensive phase in this study is 4 months. • The authors conclude “there were no significant differences of both primary failure rate and 5

	year actuarial remission rate of the two regimens. The 6 month regimen is recommended as the initial treatment of tuberculous lymphadenopathy”.
Citation	
NCC CC ID (Ref Man)	184

Evidence Table	
MGTO 1: In patients with peripheral lymph node TB on drug treatment, are regimens of six months duration as effective as regimens of other durations in eradicating TB infection?	
Bibliographic reference	Loenhout-Rooyackers, J. H., Laheij, R. J., Richter, C., & Verbeek, A. L. 2000, "Shortening the duration of treatment for cervical tuberculous lymphadenitis", <i>European Respiratory Journal</i> , vol. 15, no. 1, pp. 192-195.
Study type	Meta-analysis
Study objective	To determine the optimal duration of treatment for patients with tuberculous lymphadenitis.
Evidence level	1-
Number of patients	N=634 Studies included: Cheung 1990 (N=123), Jawahar 1990 (N=175), Kumar 1990 (N=27), Campbell 1992 (N=136), Campbell 1993 (N=136), Yuen 1997 (N=113), McCarthy 1989 (N=57), Pang 1992 (N=13) Setting: Study settings not reported.
Patient characteristics	Studies on patients with active pulmonary parenchymal disease (but not isolated mediastinal lymphadenopathy) or active TB at sites other than lymph nodes, were excluded. Furthermore, patients with concomitant renal, hepatic or haematological disease and patients who had previously received >1 month of treatment for TB or who had missed >14 consecutive or cumulative doses, were excluded from the analysis.
Intervention	All of the retrieved publications were screened for the following inclusion criteria: 1) isoniazid, rifampicin and pyrazinamide had been included in the treatment schedule, possibly with ethambutol and /or streptomycin in adequate doses, 2) treatment had been applied daily or intermittently, supervised or self-administered 3) tablets of proven bioavailability had been used 4) the diagnosis had been confirmed either by detection of acid-fast bacilli in direct smears from fine needle aspiration or from biopsy and/or by positive mycobacterial culture of biopsy and/or by histological evidence of caseating or necrotizing granulomas 5) cases were not resistant to rifampicin and pyrazinamide 6) follow-up after the end of treatment had to be at least 12 months. 6 month vs. 9 month treatment regimens were compared.
Length of follow-up	At least 12 months
Outcome measures	Relapse defined as recurrence of a residual lymph node or the appearance of a new lymph node confirmed to be tuberculous after one full course of medication with a period of clinical remission.

Effect size	<ul style="list-style-type: none"> • A total of 534 patients completed treatment and follow-up as planned. After a mean follow-up of 29 months, nodes were still present in 41/378=11%. • The number of patients with a relapse on clinical grounds after successful treatment of 6 months duration was 13/422=3.3% (95%CI 1.7 to 5.5 mean follow-up 31 months). After 9 months of therapy, 3/112=2.7% (95%CI 0.6 to 7.8, mean follow-up 20 months) relapsed. In three out of these 16 patients the relapse was bacteriologically confirmed, while in four it was histologically proven. Five patients relapsed during the first year, three patients relapsed later, and in eight patients there was no further information.
Source of funding	Not reported.
Additional comments	<ul style="list-style-type: none"> • This analysis has a limited search strategy and does not consider the quality of the eight studies it has included. • Although the study describes itself as a meta-analysis it does not use the usual techniques (i.e. fixed or random effects models). It combines evidence from different study designs (e.g. randomised trials and case series studies) and studies in adults and children and does not consider heterogeneity. • The dose of anti-tuberculous drugs used varied and was not reported in one study. • Other outcomes are reported but not for each treatment duration (e.g. occurrence of new or enlargement of existing nodes during treatment). • Mean follow-up duration is different for the two groups. • The authors conclude “six months therapy is probably sufficient for patients with tuberculous lymphadenitis”.
NCC CC ID (Ref Man)	19780

Evidence Table

MGTO2: In patients with TB of the spine on drug treatment, are regimens of six months duration as effective as regimens of longer durations in eradicating TB disease?

Bibliographic reference	1999, "Five-year assessment of controlled trials of short-course chemotherapy regimens of 6, 9 or 18 months' duration for spinal tuberculosis in patients ambulatory from the start or undergoing radical surgery. Fourteenth report of the Medical Research Council Working Party on Tuberculosis of the Spine", <i>International Orthopaedics</i> , vol. 23, pp. 73-81. Ref ID: 19732
Study type	Randomised controlled trial (Madras)
Evidence level	2+
Study objective	To compare ambulant short-course chemotherapy (for 6 or 9 months) with anterior spinal fusion plus short-course chemotherapy for spinal tuberculosis without paraplegia.
Number of patients	N= 304 N = 250 included in analysis Setting: Madras Sites: 6 Surgeons: 9
Patient characteristics	Patients with clinical and radiographic evidence of active tuberculosis of any vertebral body from first thoracic to first sacral inclusive. Patients were ineligible if they had serious extra-spinal disease likely to affect their management or response to treatment or if they gave a history of previous anti-tuberculosis chemotherapy for 12 months or more. They were also ineligible if they had paralysis severe enough to prevent their walking across a room (3-6 metres). Age: 0-14 n= 84, 15-54 n=158, >55 n = 8 Sinus and/or clinically evident abscess n = 49 Radiographic abscess shadow n = 142 Myelopathy n = 19 (with functional impairment n = 19) Radiographic site of lesion: thoracic n = 93, thoraco-lumbar n = 33, lumbar or lumbo-sacral n =124 Number of vertebra involved: 1 or 2 n = 172, 3 or 4 n=69, 5 or more n = 9 Total vertebral loss: <1 n = 180, 1-2 n = 69, > 3 n = 0 Angle of kyphosis: 0-20 n = 35, 21-40 n = 67, 41 or more n = 20
Intervention	N=82 Ambulatory Chemotherapy – 6 months of daily isoniazid (6 mg/kg body weight) plus rifampicin

	(15 mg/kg body weight) (n=82)
Comparison	N=86 Ambulatory Chemotherapy – 9 months of daily isoniazid (6 mg/kg body weight) plus rifampicin (15 mg/kg body weight) (n=86)
Length of follow-up	Assessed monthly for first 3 months, 3 monthly up to 24 months, then 6 monthly to 5 years.
Outcome measures	Primary outcome - Favourable status at five years defined as full physical activity with radiographically quiescent disease, with neither sinuses nor clinically evident abscesses and with no myelopathy with functional impairment and no modification of the allocated regimen. Occurrence of bony fusion Changes in total vertebral body loss and angle of kyphosis from 0 to 5 years
Effect size	<p><u>Status at five years</u></p> <p>6 month regimen 91% of patients had favourable status 2% still not favourable: not quiescent radiographically 0% death due to or associated with spinal disease 6% needed additional chemotherapy and/or surgery for spinal disease 0% had radical operation abandoned</p> <p>9 month regimen 98% of patients had favourable status 1% still not favourable: not quiescent radiographically 0% death due to or associated with spinal disease 1% needed additional chemotherapy and/or surgery for spinal disease 0% had radical operation abandoned</p> <p>Cumulative % of patients with bony fusion 6 months –15% of 6 month regimen patients, 15% of 9 month regimen patients 12 months –33% of 6 month regimen patients, 29% of 9 month regimen patients 24 months – 52% of 6 month regimen patients, 51% of 9 month regimen patients 36 months –66% of 6 month regimen patients, 58% of 9 month regimen patients 42 months –67% of 6 month regimen patients, 62% of 9 month regimen patients 48 months –70% of 6 month regimen patients, 66% of 9 month regimen patients 54 months – 70% of 6 month regimen patients, 72% of 9 month regimen patients 60 month - 75% of 6 month regimen patients, 74% of 9 month regimen patients</p>

Changes in total vertebral body loss and angle of kyphosis from 0 to 5 years

6 month regimen

0% of patients showed a reduction in vertebral body loss

51% of patients showed no change

20% of patients showed an increase in vertebral body loss of 0.25-0.49 vertebral bodies

24% of patients showed an increase in vertebral body loss of 0.5-0.99

5% of patients showed an increase in vertebral body loss of 1 or more

9 month regimen

0% of patients showed a reduction in vertebral body loss

65% of patients showed no change

16% of patients showed an increase in vertebral body loss of 0.25-0.49 vertebral bodies

16% of patients showed an increase in vertebral body loss of 0.5-0.99

4% of patients showed an increase in vertebral body loss of 1 or more

Angle of Kyphosis

6 month regimen

0% of patients showed a reduction in kyphosis

58% of patient showed no change in angle of kyphosis

36% of patients showed an increase in angle of kyphosis of 11°-30°

2% of patients showed an increase in angle of kyphosis of 31° or more

9 month regimen

4% of patients showed a reduction in kyphosis

51% of patient showed no change in angle of kyphosis

35% of patients showed an increase in angle of kyphosis of 11°-30°

10% of patients showed an increase in angle of kyphosis of 31° or more

Conclusions:

At five years, 75/82 in the 6-month group and 84/86 in 9 month group had a favourable status.

Rate of occurrence of bony fusion was similar in both groups.

Mean total vertebral loss on admission was 0.83 for 6 month and 0.65 for 9 month group. At five years, mean further loss of 0.35 and 0.24 vertebral bodies respectively.

	Mean increase in angle of kyphosis was 11.9° in the 6 month group and 10.5° in the 9-month group.
Source of Funding	Not stated
Additional comments	<ul style="list-style-type: none"> • No statistical tests. • Dosage schedules of both isoniazid and rifampicin were modified because of the occurrence of jaundice in 18 patients receiving relatively high doses. • Not intention to treat. 250/304 included in analysis. Reasons for exclusions provided in earlier publication. • Baseline characteristics similar between groups (data not shown). • Diagnosis of tuberculosis confirmed (data in previous publication). • Randomisation method described in previous publication (sealed enveloped). • Blinding of investigators not discussed. • Modifications to treatment regimen discussed. • Patient compliance not addressed.
Citation	
NCC CC ID (Ref Man)	19732 (same population 19744) Ten year follow-up in ref 19737

Evidence Table

MGTO2: In patients with TB of the spine on drug treatment, are regimens of six months duration as effective as regimens of longer durations in eradicating TB disease?

Bibliographic reference	1999, "Five-year assessment of controlled trials of short-course chemotherapy regimens of 6, 9 or 18 months' duration for spinal tuberculosis in patients ambulatory from the start or undergoing radical surgery. Fourteenth report of the Medical Research Council Working Party on Tuberculosis of the Spine", <i>International Orthopaedics</i> , vol. 23, pp. 73-81. Ref ID: 19732
Study type	Randomised controlled trial (Hong Kong)
Evidence level	2+
Study objective	To compare isoniazid and rifampicin daily for 6 or 9 months combined with radical surgical resection with bone grafting and streptomycin for 6 months.
Number of patients	N= 60 patients N = 50 patients for 5 year analysis Setting: Hong Kong Sites:1 Surgeons: 3
Patient characteristics	Patients with clinical and radiographic evidence of active tuberculosis of any vertebral body from first thoracic to first sacral inclusive. Patients were ineligible if they had serious extra-spinal disease likely to affect their management or response to treatment or if they gave a history of previous anti-tuberculosis chemotherapy for 12 months or more. Age: 0-14 n= 13, 15-54 n=28, >55 n = 9 Sinus and/or clinically evident abscess n = 7 Radiographic abscess shadow n = 29 Myelopathy n = 2 (with functional impairment n = 0) Radiographic site of lesion: thoracic n = 18, thoraco-lumbar n = 4, lumbar or lumbo-sacral n =28 Number of vertebra involved: 1 or 2 n = 44, 3 or 4 n=5, 5 or more n = 1 Total vertebral loss: <1 n = 47, 1-2 n = 3, > 3 n = 0 Angle of kyphosis: 0-20 n = 10, 21-40 n = 8, 41 or more n = 2
Intervention	N=24 Surgery (radical resection and bone graft) and chemotherapy (6months): isoniazid (6mg/kg) plus rifampicin (15mg/kg) in one dose daily plus streptomycin twice a week for 6 months

Comparison	N=26 Surgery (radical resection and bone graft) and chemotherapy (9months): isoniazid (6mg/kg) plus rifampicin (15mg/kg) in one dose daily for 9 months plus streptomycin twice a week for 6 months
Length of follow-up	Assessed monthly for first 3 months, 3 monthly up to 24 months, then 6 monthly to 3 years.
Outcome measures	Primary outcome - Favourable status at five years defined as full physical activity with radiographically quiescent disease, with neither sinuses nor clinically evident abscesses and with no myelopathy with functional impairment and no modification of the allocated regimen. Occurrence of bony fusion Changes in total vertebral body loss and angle of kyphosis from 0 to 5 years
Effect size	<p><u>Status at five years</u></p> <p>6 month regimen 96% of patients had favourable status 4% needed additional chemotherapy and/or surgery for spinal disease</p> <p>9 month regimen 96% of patients had favourable status 4% needed additional chemotherapy and/or surgery for spinal disease</p> <p>Cumulative % of patients with bony fusion 6 months – 38% of 6 month regimen patients, 42% of 9 month regimen patients 12 months – 58% of 6 month regimen patients, 81% of 9 month regimen patients 24 months – 92% of 6 month regimen patients, 96% of 9 month regimen patients 36-60 months – 100% of both groups had bony fusion</p> <p><u>Changes in total vertebral body loss and angle of kyphosis from 0 to 5 years</u></p> <p>6 month regimen 8% patients showed a reduction in vertebral body loss 54% of patients showed no change 21% of patients showed an increase in vertebral body loss of 0.25-0.49 vertebral bodies 17% of patients showed an increase in vertebral body loss of 0.5-0.99 0% of patients showed an increase in vertebral body loss of 1 or more</p> <p>9 month regimen</p>

	<p>20% of patients showed a reduction in vertebral body loss 56% of patients showed no change 16% of patients showed an increase in vertebral body loss of 0.25-0.49 vertebral bodies 8% of patients showed an increase in vertebral body loss of 0.5-0.99 0% of patients showed an increase in vertebral body loss of 1 or more</p> <p>Angle of Kyphosis</p> <p>6 month regimen 0% patients showed a reduction in kyphosis 36% of patients showed no change 64% of patients showed an increase in angle of kyphosis of 11°-30° 0% of patients showed an increase in angle of kyphosis of 31° or more</p> <p>9 month regimen 7% of patients showed a reduction in kyphosis 79% of patient showed no change in angle of kyphosis 14% of patients showed an increase in angle of kyphosis of 11°-30° 0% of patients showed an increase in angle of kyphosis of 31° or more</p> <p>Authors conclusions: All patients (except one in each group) in both groups had a favourable status clinically and radiographically at 5 years, most of whom had achieved favourable status by 3 years. Complete bony fusion was present at 3 years in both groups.</p> <p>Mean total vertebral body loss in both groups was 0.50; at 5 years there was a further mean loss of 0.15 vertebral bodies in 6 month group and 0.05 in 9 month group. By 5 years the mean increase in kyphosis was 12.5 for 6 month group, with a mean decrease of 1.6 for the 9 month group.</p>
Source of Funding	Not stated
Additional comments	<ul style="list-style-type: none"> • Authors state that 'clinical and radiographic condition of the two groups on admission was broadly similar' – data not shown. • Reasons for exclusion provided. • No statistical tests. • Not intention to treat – 50/60 patients included in analysis.

	<ul style="list-style-type: none"> • Diagnosis of tuberculosis confirmed (data in previous publication). • Randomisation method described in previous publication (sealed enveloped). • Blinding of investigators not discussed. • Modifications to treatment regimen discussed. • Side effects not discussed. • Radiographs read by one investigator. • Patient compliance addressed as chemotherapy supervised daily on outpatient basis.
Citation	
NCC CC ID (Ref Man)	19732 (some information from 276 – 3 year results)

Evidence Table

MGTO2: In patients with TB of the spine on drug treatment, are regimens of six months duration as effective as regimens of longer durations in eradicating TB disease?

Bibliographic reference	1999, "Five-year assessment of controlled trials of short-course chemotherapy regimens of 6, 9 or 18 months' duration for spinal tuberculosis in patients ambulatory from the start or undergoing radical surgery. Fourteenth report of the Medical Research Council Working Party on Tuberculosis of the Spine", <i>International Orthopaedics</i> , vol. 23, pp. 73-81. Ref ID: 19732
Study type	Randomised controlled trial (Korea)
Evidence level	2-
Study objective	To compare status at five years in patients with TB of the spine in patients receiving 6 or 9 months isoniazid and rifampicin, or 9 or 18 months isoniazid plus ethambutol or isoniazid plus
Number of patients	N= 359 N = 151 included in 3 year analysis Setting: Korea Sites: 4 Surgeons:
Patient characteristics	Patients with clinical and radiographic evidence of active tuberculosis of any vertebral body from first thoracic to first sacral inclusive. Patients were ineligible if they had serious extra-spinal disease likely to affect their management or response to treatment or if they gave a history of previous anti-tuberculosis chemotherapy for 12 months or more. They were also ineligible if they had paralysis severe enough to prevent their walking across a room (3-6 metres). Age: 0-14 n= 88, 15-54 n=60, >55 n = 3 Sinus and/or clinically evident abscess n = 49 Radiographic abscess shadow n = 93 Myelopathy n = 19 (with functional impairment n = 11) Radiographic site of lesion: thoracic n = 62, thoraco-lumbar n = 32, lumbar or lumbo-sacral n =57 Number of vertebra involved: 1 or 2 n = 63, 3 or 4 n=58, 5 or more n = 30 Total vertebral loss: <1 n = 65, 1-2 n = 66, > 3 n = 13 Angle of kyphosis: 0-20 n = 8, 21-40 n = 38, 41 or more n = 34
Intervention	N=39 Ambulatory Chemotherapy – 6 months of daily isoniazid (6 mg/kg body weight) plus rifampicin (15 mg/kg body weight) plus streptomycin 20mg/kg

Comparison	<p>N=40 Ambulatory Chemotherapy (AC9) – 9 months of daily isoniazid (6 mg/kg body weight) plus rifampicin (15 mg/kg body weight) plus streptomycin 20mg/kg</p> <p>Or</p> <p>N=33 Ambulatory Chemotherapy (AC9PE) – 9 months of daily isoniazid (6 mg/kg body weight) plus ethambutol 15-25mg/kg or PAS 0.2 g/kg</p> <p>Or</p> <p>N=39 Ambulatory Chemotherapy (AC18PE) – 18 months of daily isoniazid (6 mg/kg body weight) plus ethambutol 15-25mg/kg or PAS 0.2g/kg</p>
Length of follow-up	Assessed monthly for first 3 months, 3 monthly up to 24 months, then 6 monthly to 3 years.
Outcome measures	<p>Primary outcome - Favourable status defined as full physical activity with radiographically quiescent disease, with neither sinuses nor clinically evident abscesses and with no myelopathy with functional impairment and no modification of the allocated regimen.</p> <p>Occurrence of bony fusion</p> <p>Changes in total vertebral body loss and angle of kyphosis from 0 to 5 years</p>
Effect size	<p><u>Status at five years</u></p> <p>AC6</p> <p>90% of patients had favourable status</p> <p>8% still not favourable: not quiescent radiographically</p> <p>3% had sinus present</p> <p>AC 9</p> <p>85% of patients had favourable status</p> <p>12% still not favourable: not quiescent radiographically</p> <p>0% death due to or associated with spinal disease</p> <p>2% needed additional chemotherapy and/or surgery for spinal disease</p> <p>0% had radical operation abandoned</p> <p>AC 9 PE</p> <p>73% of patients had favourable status</p>

	<p>3% still not favourable: not quiescent radiographically 0% death due to or associated with spinal disease 3% had sinus present 21% needed additional chemotherapy and/or surgery for spinal disease 0% had radical operation abandoned</p> <p>AC18PE 90% of patients had favourable status 10% still not favourable: not quiescent radiographically 0% death due to or associated with spinal disease 0% had sinus present 0% needed additional chemotherapy and/or surgery for spinal disease 0% had radical operation abandoned</p> <p>Cumulative % of patients with bony fusion 6 months – 8% of AC6 patients, 0% of AC9 patients, 9% of AC9PE patients, 5% of AC9PE patients, 15% of AC18 patients 12 months – 18% of AC6 patients, 3% of AC9 patients, 21% of AC9PE patients, 11% of AC18PE patients 24 months – 37% of AC6 patients, 31% of AC9 patients, 33% of AC9PE patients, 35% of AC18PE patients 36 months – 47% of AC6 patients, 36% of AC9 patients, 39% of AC9PE patients, 46% of AC18PE patients 42 months – 50% of AC6 patients, 39% of AC9 patients, 39% of AC9PE patients, 49% of AC18PE patients 48 months – 53% of AC6 patients, 44% of AC9 patients, 39% of AC9PE patients, 49% of AC18PE patients 54 months – 55% of AC6 patients, 53% of AC9 patients, 42% of AC9PE patients, 51% of AC18PE patients 60 month - 58% of AC6 patients, 56% of AC6 patients, 48% of AC9 patients, 62% of AC18PE patients</p> <p><u>Changes in total vertebral body loss and angle of kyphosis from 0 to 5 years</u> AC6 3% patients showed a reduction in vertebral body loss</p>
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	<p>53% of patients showed no change 8% of patients showed an increase in vertebral body loss of 0.25-0.49 vertebral bodies 25% of patients showed an increase in vertebral body loss of 0.5-0.99 11% of patients showed an increase in vertebral body loss of 1 or more</p> <p>AC9 0% of patients showed a reduction in vertebral body loss 31% of patients showed no change 16% of patients showed an increase in vertebral body loss of 0.25-0.49 vertebral bodies 38% of patients showed an increase in vertebral body loss of 0.5-0.99 16% of patients showed an increase in vertebral body loss of 1 or more</p> <p>AC9PE 6% of patients showed a reduction in vertebral body loss 23% of patients showed no change 16% of patients showed an increase in vertebral body loss of 0.25-0.49 vertebral bodies 19% of patients showed an increase in vertebral body loss of 0.5-0.99 36% of patients showed an increase in vertebral body loss of 1 or more</p> <p>AC18PE 6% of patients showed a reduction in vertebral body loss 31% of patients showed no change 16% of patients showed an increase in vertebral body loss of 0.25-0.49 vertebral bodies 34% of patients showed an increase in vertebral body loss of 0.5-0.99 12% of patients showed an increase in vertebral body loss of 1 or more</p> <p>Angle of Kyphosis AC6 6% patients showed a reduction in kyphosis 56% of patients showed no change 28% of patients showed an increase in angle of kyphosis of 11°-30° 11% of patients showed an increase in angle of kyphosis of 3° or more</p>
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	<p>AC9 4% of patients showed a reduction in kyphosis 38% of patient showed no change in angle of kyphosis 42% of patients showed an increase in angle of kyphosis of 11°-30° 17% of patients showed an increase in angle of kyphosis of 31° or more</p> <p>AC 9PE 0% of patients showed a reduction in kyphosis 31% of patient showed no change in angle of kyphosis 31% of patients showed an increase in angle of kyphosis of 11°-30° 38% of patients showed an increase in angle of kyphosis of 31° or more</p> <p>AC18PE 10% of patients showed a reduction in kyphosis 52% of patient showed no change in angle of kyphosis 33% of patients showed an increase in angle of kyphosis of 11°-30° 5% of patients showed an increase in angle of kyphosis of 31° or more</p> <p>Conclusions:</p> <ul style="list-style-type: none"> • 6 and 9 month regimens containing rifampicin showed better outcomes than 9 month regimens containing PAS or ethambutamol. • 6 and 9 month regimens containing rifampicin had similar outcomes to 18 month regimens containing PAS or ethambutamol. • At 3 years, complete bony fusion was present in only . 47% of AC6 patients, 36% of AC9 patients, 39% of AC9PE patients, 46% of AC18 patients. At five years bony fusion occurred in 58% of AC6 patients, 56% of AC6 patients, 48% of AC9 patients, 62% of AC18PE patients
Source of Funding	Not stated
Additional comments	<ul style="list-style-type: none"> • No statistics • Reasons for exclusion discussed; however, 208/359 patients were not included in this analysis • Results restricted to those patients seen at month 53 or later • Follow-up terminated early due to investigator leaving project. • Authors stated 'Characteristics of the groups were similar' (data not shown) • Treatment was on outpatient basis

	<ul style="list-style-type: none"> • Tuberculosis diagnosis confirmed. • Treatment failure rates were 3% in patients given isoniazid plus rifampicin, 6% with 18 months of treatment and 19% with 9 months of treatment. • 58% of patients were children • Results of PAS or ethambutamol groups were combined as they were similar
Citation	
NCC CC ID (Ref Man)	19732

Evidence Table

MGTO2: In patients with TB of the spine on drug treatment, are regimens of six months duration as effective as regimens of longer durations in eradicating TB disease?

Bibliographic reference	Parthasarathy, R., Sriram, K., Santha, T., Prabhakar, R., Somasundaram, P. R., & Sivasubramanian, S. 1999, "Short-course chemotherapy for tuberculosis of the spine. A comparison between ambulant treatment and radical surgery - Ten-year report", <i>Journal of Bone & Joint Surgery - British Volume</i> , vol. 81, no. 3, pp. 464-471. Ref ID: 19737
Study type	Randomised controlled trial (Madras)
Evidence level	2++
Study objective	To compare ambulant short-course chemotherapy (6 months or 9 months) with anterior spinal fusion plus short-course chemotherapy for spinal TB without paraplegia
Number of patients	N= 304 N = 235 included in analysis with (78 patients not reported here as in the surgery arm) Setting: Madras Sites: 6 Surgeons: 9
Patient characteristics	Patients admitted to study with clinical and radiographic evidence of active tuberculosis of any vertebral body from first thoracic to first sacral inclusive. Patients were ineligible if they had paralysis of the lower limbs severe enough to prevent them from walking across a room, serious extraspinal disease (tuberculous or non-tuberculous) a history of previous specific chemotherapy for 12 months or more, or had already had major surgery for the spinal disease. Age (years): 0-14 (AC6 - 45%, AC9 - 28%), 15-34 (AC 6 - 38%, AC 9 - 39%), >35 (AC 6 - 17%, AC9 - 33%) Site of lesion: thoracic (AC6 - 37%, AC9 – 41%), thoracolumbar (AC6 – 15%, AC9 – 11%), lumbar (AC6 - 42%, AC9 39%), lumbosacral (AC6 - 5%, AC9 - 9%) Angle of kyphosis: 0-30 (AC 6 -56%, AC9 – 65%), 31-60 (AC6 - 44%, AC9 – 35%)
Intervention	N=78 Ambulatory Chemotherapy – 6 months of daily isoniazid (6 mg/kg body weight) plus rifampicin (15 mg/kg body weight)
Comparison	N=79 Ambulatory Chemotherapy – 9 months of daily isoniazid (6 mg/kg body weight) plus rifampicin (15 mg/kg body weight)

Length of follow-up	Assessed monthly for first 3 months, 3 monthly up to 24 months, then 6 monthly to 10 years.
Outcome measures	Deaths associated with spinal tuberculosis Sinuses and/or clinically evident abscesses Involvement of central nervous system Bony fusion Angle of kyphosis Treatment completion rate
Effect size	<p>Status - Favourable status (no sinus or clinically evident abscess, no myelopathy and no modification of allocated regimen, no limitation of physical activity due to spinal lesion and radiologically quiescent disease)</p> <p>At 10 years favourable status was given to: 94% of 6-month chemotherapy group 99% of 9-month chemotherapy group This difference was not significant (p=0.2)</p> <p>At 10 years unfavourable status was given to: 6% of 6-month chemotherapy group 1% of 9-month chemotherapy group</p> <p><u>Bony fusion</u> At 10 years, complete bony fusion occurred in: 81% of 6-month chemotherapy group 85% of 9-month chemotherapy group No significant difference between groups</p> <p>At 10 years, partial bony fusion occurred in: 14% of 6-month and 9-month chemotherapy group</p> <p><u>Angle of kyphosis</u> Angle of kyphosis increased in both treatment groups with no significant difference between groups; however, in patients less than 15 years of age with angle of kyphosis >30°, the mean increase by ten years was 30°, compared with 10° in those >15 years (p=0.001)</p>

Source of Funding	Not stated
Additional comments	<ul style="list-style-type: none"> • Dosage schedules of both isoniazid and rifampicin were modified because of the occurrence of jaundice in 18 patients receiving relatively high doses. • 235/304 included in analysis. Reasons for exclusions provided in earlier publication. Equal proportions (23%) excluded from each arm. • Baseline characteristics similar between groups (data not shown). • Diagnosis of tuberculosis confirmed (data in previous publication). • Randomisation method described in previous publication (sealed enveloped). • Blinding of investigators not discussed. • Modifications to treatment regimen discussed. • Patient compliance not addressed.
Citation	
NCC CC ID (Ref Man)	19737 (same population as 19732 Madras at 5 years)

Evidence Table

MGTO2: In patients with TB of the spine on drug treatment, are regimens of six months duration as effective as regimens of longer durations in eradicating TB disease?

Bibliographic reference	Upadhyay, S. S., Saji, M. J., & Yau, A. C. 1996, "Duration of antituberculosis chemotherapy in conjunction with radical surgery in the management of spinal tuberculosis", <i>Spine</i> , vol. 21, no. 16, pp. 1898-1903. Ref ID: 19743
Study type	Randomised controlled trial (evaluated as a cohort study)
Evidence level	2+
Study objective	To evaluate the efficacy of short-course antituberculous chemotherapy in relation to the standard 18-month chemotherapy in conjunction with radical surgery for TB of the spine.
Number of patients	N=123 (N=114 available for mean follow-up of 14.6 years) Setting: Hong Kong
Patient characteristics	These patients were the subjects of the MRC prospective study (1966 to 1978) and were selected on the basis of having clinical and radiologic evidence of TB of the spine anywhere from T1 to S1 (both inclusive). Patients with severe extra-spinal disease (that would affect the management of spinal lesion), paralysis severe enough to prevent walking across the room, history of previous antituberculosis chemotherapy for 12 months or more or a vertebral destruction equivalent to three or more vertebral bodies were not entered in this prospective study. Age (years): 6 month regimen : 32.6 ± 18.3, 9 month regimen : 28.5 ± 19.6, 18 month regimen 21.2 ± 16.7 Sex (M:F): SC6 – 9:16, SC9 - 16:10, SC 18 - 30:33 Incidence of pulmonary tuberculosis: SC6 – 5 (20%), SC9 – 13 (50%), SC18 – 10 (16%)
Intervention	N=25 Surgery and chemotherapy – Hong Kong radical resection with bone grafting plus 6 months of daily isoniazid (6mg/kg body weight) plus rifampicin (up to 20mg/kg body weight) plus streptomycin (20mg/kg)
Comparison	N=26 Surgery and chemotherapy - Radical resection with bone grafting plus 9 months of daily isoniazid (6mg/kg body weight) plus rifampicin (up to 20mg/kg body weight) plus streptomycin (20mg/kg)

	N=63 Surgery and chemotherapy - Radical resection with bone grafting plus 18 months of daily isoniazid (6mg/kg body weight) plus sodium PAS (0.2g/kg) plus streptomycin (20mg/kg)
Length of follow-up	At 1 month intervals up to 3 months postoperatively, 3-month intervals up to 30 months, 6 month intervals up to 5 years and thereafter at 12 month intervals (minimum follow-up 10 years). Average 14.6 years
Outcome measures	Neurologic status Change in mean angle of deformity. All lateral spinal radiographs obtained on each visit were measured for deformity angle using an electronic digitiser. Side effects
Effect size	<ul style="list-style-type: none"> • Clinical outcome -Neurologic status: Clinical outcome was similar in all treatment groups. At final follow-up evaluation, one patient in the 6 months chemotherapeutic group had minor motor deficits of the dorsiflexor of the ankles and feet, whereas one patient in the 18 months group had partial unilateral sensory deficits, along the distribution of L4 and L5 dermatomes. Abnormal reflexes were present at final follow-up evaluation in 18%, 8% and 10% of patients respectively for the 6, 9 and 18 month regimens (absence of knee and ankle jerks mainly). No patients had bladder or bowel disturbances at final follow-up. There was no recurrence or reactivation of tuberculosis in either group. • Change in mean angle of deformity: There were no statistically significant differences in the change in mean angle of deformity between groups. • Side effects: Most side effects occurred early in treatment period and were not related to duration of treatment. Incidence of side effects in 6, 9 and 18 month groups were 24%, 19.2% and 27% respectively.
Source of Funding	Not stated
Additional comments	<ul style="list-style-type: none"> • The authors concluded that clinical outcome is equally as good with 6 month chemotherapy compared with 9 or 18 month chemotherapy. There was no risk of progression of deformity associated with 6 month chemotherapy compared with 9 or 18 month chemotherapy. • The authors note that there was a tendency toward the development of a higher incidence of abnormal reflexes between 5 years and final analysis in all groups. It is difficult to comment on the exact causation as the sample sizes in the 6 and 9 month regimens were relatively small, therefore there are limitations on drawing conclusions related to neurology. • Reasons for exclusion from analysis provided. • Small group sizes in 6 and 9 month treatment groups. • Mean age in 18 month group appears to be significantly lower than in 6 month group

	<ul style="list-style-type: none"> • Only 77 patients were randomised. First 37 patients before randomisation received chemotherapy for 18 months. • Authors state that extent of disease at entry and duration of antituberculous chemotherapy before surgery was similar in the three groups • Surgical methods and spinal measurements described fully. • No discussion of confirmation of diagnosis • No intention to treat analysis. • No statistical comparison between characteristics of patients in individual groups. • Randomisation method not described. • Investigators did not state whether tests performed blindly or independently. • Not stated whether investigators at different sites used same methodology. • Follow-up times vary between patients – minimum follow-up 10 years, average follow-up 14.6 years
Citation	
NCC CC ID (Ref Man)	19743

Evidence Table

MGTO3: In patients with TB of the spine, is surgery with short course chemotherapy more effective than short course chemotherapy alone in eradicating TB disease?

Bibliographic reference	1999, "Five-year assessment of controlled trials of short-course chemotherapy regimens of 6, 9 or 18 months' duration for spinal tuberculosis in patients ambulatory from the start or undergoing radical surgery. Fourteenth report of the Medical Research Council Working Party on Tuberculosis of the Spine", <i>International Orthopaedics</i> , vol. 23, pp. 73-81. Ref ID: 19732
Study type	Randomised controlled trial (Madras)
Evidence level	2++
Study objective	To compare ambulant short-course chemotherapy with anterior spinal fusion plus short-course chemotherapy for spinal tuberculosis without paraplegia.
Number of patients	N= 304 patients with clinical and radiographic evidence of active tuberculosis of any vertebral body from first thoracic to first sacral inclusive. N = 250 available for five year analysis Setting: Madras Sites: 6 Surgeons: 9
Patient characteristics	Patients with clinical and radiographic evidence of active tuberculosis of any vertebral body from first thoracic to first sacral inclusive. Patients were ineligible if they had serious extra-spinal disease likely to affect their management or response to treatment or if they gave a history of previous anti-tuberculosis chemotherapy for 12 months or more. They were also ineligible if they had paralysis severe enough to prevent their walking across a room (3-6 metres). Age: 0-14 n= 84, 15-54 n=158, >55 n = 8 Sinus and/or clinically evident abscess n = 49 Radiographic abscess shadow n = 142 Myelopathy n = 19 (with functional impairment n = 19) Radiographic site of lesion: thoracic n = 93, thoraco-lumbar n = 33, lumbar or lumbo-sacral n =124 Number of vertebra involved: 1 or 2 n = 172, 3 or 4 n=69, 5 or more n = 9 Total vertebral loss: <1 n = 180, 1-2 n = 69, > 3 n = 0 Angle of kyphosis: 0-20 n = 35, 21-40 n = 67, 41 or more n = 20
Intervention	N=77 Surgery And Chemotherapy (SC) - Radical anterior resection with bone grafting plus 6 months

	of daily isoniazid (6mg/kg body weight) plus rifampicin (15 mg/kg body weight)
Comparison	<p>N=79 Ambulatory Chemotherapy (AC6) – 6 months of daily isoniazid (6 mg/kg body weight) plus rifampicin (15 mg/kg body weight)</p> <p>Or</p> <p>N=85 Ambulatory Chemotherapy (AC9) – 9 months of daily isoniazid (6 mg/kg body weight) plus rifampicin (15 mg/kg body weight)</p>
Length of follow-up	Assessed monthly for first 3 months, 3 monthly up to 24 months, then 6 monthly to 5 years.
Outcome measures	<p>Occurrence of bony fusion</p> <p>Changes in total vertebral body loss and angle of kyphosis from 0 to 5 years</p> <p>Status at five years defined as no sinus or clinically evident abscess, no myelopathy and no modification of allocated regimen, no limitation of physical activity due to spinal lesion and radiologically quiescent disease)</p>
Effect size	<p>Cumulative % of patients with bony fusion</p> <p>6 months – 10% of SC patients, 15% of AC6 patients, 15% of AC9 patients</p> <p>12 months – 34% of SC patients, 33% of AC6 patients, 29% of AC9 patients</p> <p>24 months – 55% of SC patients, 52% of AC6 patients, 51% of AC9 patients</p> <p>36 months – 65% of SC patients, 66% of AC6 patients, 58% of AC9 patients</p> <p>42 months – 68% of SC patients, 67% of AC6 patients, 62% of AC9 patients</p> <p>48 months – 69% of SC patients, 70% of AC6 patients, 66% of AC9 patients</p> <p>54 months – 73% of SC patients, 70% of AC6 patients, 72% of AC9 patients</p> <p>60 month - 77% of SC patients, 75% of AC6 patients, 74% of AC9 patients</p> <p><u>Changes in total vertebral body loss and angle of kyphosis from 0 to 5 years</u></p> <p>SC</p> <p>7% patients showed a reduction in vertebral body loss</p> <p>61% of patients showed no change</p> <p>15% of patients showed an increase in vertebral body loss of 0.25-0.49 vertebral bodies</p> <p>3% of patients showed an increase in vertebral body loss of 0.5-0.99</p> <p>AC6</p> <p>0% of patients showed a reduction in vertebral body loss</p>

	<p>51% of patients showed no change 20% of patients showed an increase in vertebral body loss of 0.25-0.49 vertebral bodies 24% of patients showed an increase in vertebral body loss of 0.5-0.99 5% of patients showed an increase in vertebral body loss of 1 or more</p> <p>AC9 0% of patients showed a reduction in vertebral body loss 65% of patients showed no change 16% of patients showed an increase in vertebral body loss of 0.25-0.49 vertebral bodies 16% of patients showed an increase in vertebral body loss of 0.5-0.99 4% of patients showed an increase in vertebral body loss of 1 or more</p> <p>Angle of Kyphosis</p> <p>SC 3% patients showed a reduction in kyphosis 62% of patients showed no change 32% of patients showed an increase in angle of kyphosis of 11°-30° 6% of patients showed an increase in angle of kyphosis of 3° or more</p> <p>AC 6 0% of patients showed a reduction in kyphosis 58% of patient showed no change in angle of kyphosis 36% of patients showed an increase in angle of kyphosis of 11°-30° 2% of patients showed an increase in angle of kyphosis of 31° or more</p> <p>AC 9 4% of patients showed a reduction in kyphosis 51% of patient showed no change in angle of kyphosis 35% of patients showed an increase in angle of kyphosis of 11°-30° 10% of patients showed an increase in angle of kyphosis of 31° or more</p> <p><u>Status at five years</u> SC</p>
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	<p>88% of patients had favourable status 2% still not favourable: not quiescent radiographically 5% death due to or associated with spinal disease 2% needed additional chemotherapy and/or surgery for spinal disease 2% had radical operation abandoned</p> <p>AC 6 91% of patients had favourable status 2% still not favourable: not quiescent radiographically 0% death due to or associated with spinal disease 6% needed additional chemotherapy and/or surgery for spinal disease 0% had radical operation abandoned</p> <p>AC 9 98% of patients had favourable status 1% still not favourable: not quiescent radiographically 0% death due to or associated with spinal disease 1% needed additional chemotherapy and/or surgery for spinal disease 0% had radical operation abandoned</p> <p>Conclusions: Radical surgery in addition to chemotherapy shows no benefit over 6 months or 9 months of chemotherapy alone using the following outcomes: occurrence of bony fusion, changes in total vertebral body loss and angle of kyphosis from 0 to 5 years or status at five years.</p>
Source of Funding	Not stated
Additional comments	<ul style="list-style-type: none"> • Radiographs, sputum, pus and urine samples used to detect active tuberculosis. • Surgery consisted of radical excision of tuberculous focus and repair of resultant gap with autologous bone grafts. • Details of assessment described in previous publication • Reasons for exclusion from 5 year and 10 year analysis given. • No intention to treat analysis.

	<ul style="list-style-type: none"> • No statistical comparison between characteristics of patients in individual groups. Authors stated that the distributions of the patients were broadly similar in the three groups. • Investigators did not state whether tests performed blindly or independently. • Not stated whether investigators at different sites used same methodology. • Isoniazid and rifampicin alone are not standard treatment in the UK. • Chemotherapy toxicity not discussed.
Citation	
NCC CC ID (Ref Man)	19732 (same population as 19737 which reports ten year results)

Evidence Table

MGTO3: In patients with TB of the spine, is surgery with short course chemotherapy more effective than short course chemotherapy alone in eradicating TB disease?

Bibliographic reference	Parthasarathy, R., Sriram, K., Santha, T., Prabhakar, R., Somasundaram, P. R., & Sivasubramanian, S. 1999, "Short-course chemotherapy for tuberculosis of the spine. A comparison between ambulant treatment and radical surgery - Ten-year report", <i>Journal of Bone & Joint Surgery - British Volume</i> , vol. 81, no. 3, pp. 464-471. Ref ID: 19737
Study type	Randomised controlled trial
Evidence level	2++
Study objective	To compare ambulant short-course chemotherapy with anterior spinal fusion plus short-course chemotherapy for spinal TB without paraplegia
Number of patients	N=304 (n=235 available for 10 year analysis) Patients with clinically and radiologically active tuberculosis of the spine. Setting: South India Sites: 6 Surgeons: 9
Patient characteristics	Patients admitted to study with clinical and radiographic evidence of active tuberculosis of any vertebral body from first thoracic to first sacral inclusive. Patients were ineligible if they had paralysis of the lower limbs severe enough to prevent them from walking across a room, serious extraspinal disease (tuberculous or non-tuberculous) a history of previous specific chemotherapy for 12 months or more, or had already had major surgery for the spinal disease. Age (years): 0-14 (35%), 15-34 (40%), >35 (26%) Site of lesion: thoracic (37%), thoracolumbar (14%), lumbar (42%), lumbosacral (8%) Angle of kyphosis: 0-30 (60%), 31-60 (40%)
Intervention	N=78 Surgery And Chemotherapy - Radical anterior resection with bone grafting plus 6 months of daily isoniazid (5-7 mg/kg body weight) plus rifampicin (10-15 mg/kg body weight)
Comparison	N=78 Chemotherapy Alone - ambulant chemotherapy for 6 months with daily isoniazid (5-7 mg/kg) plus rifampicin (10-15 mg/kg) N=79 Chemotherapy Alone - ambulant chemotherapy for 9 months with daily isoniazid (5-7 mg/kg) plus rifampicin (10-15 mg/kg)

Length of follow-up	10 years
Outcome measures	<p>Favourable status defined as no sinus or clinically evident abscess, no myelopathy and no modification of allocated regimen, no limitation of physical activity due to spinal lesion and radiologically quiescent disease.</p> <p>Deaths associated with spinal tuberculosis Sinuses and/or clinically evident abscesses Involvement of central nervous system Bony fusion Angle of kyphosis Treatment completion rate</p>
Effect size	<p>Status -</p> <p>At 10 years favourable status was given to: 90% of surgery and chemotherapy group 94% of 6-month chemotherapy group 99% of 9-month chemotherapy group</p> <p>At 10 years unfavourable status was given to: 10% of surgery and chemotherapy group 6% of 6-month chemotherapy group 1% of 9-month chemotherapy group</p> <p>Authors concluded that the surgery and chemotherapy treatment was less effective than 9-month chemotherapy treatment ($p=0.03$), the difference being due to surgical complications.</p> <p><u>Deaths associated with spinal tuberculosis</u> Four patients died (all within first six months), all in surgery and chemotherapy group. Three died in postoperative period and the other had complications of postoperative paraplegia.</p> <p><u>Sinuses and/or clinically evident abscesses</u> Patients in the surgery and chemotherapy group had a faster resolution of sinuses and/or clinically evident abscesses ($p<0.001$ at two months) and a lower incidence ($p=0.03$) than those in the chemotherapy groups. No recurrence of lesions during 10-year period.</p> <p><u>Bony fusion</u></p>

	<p>At 10 years, complete bony fusion occurred in: 90% of surgery and chemotherapy group 81% of 6-month chemotherapy group 85% of 9-month chemotherapy group No significant difference between groups</p> <p>At 10 years, partial bony fusion occurred in: 7% of surgery and chemotherapy group 14% of 6-month and 9-month chemotherapy group</p> <p><u>Angle of kyphosis</u> Mean angles of kyphosis on admission – 26-30% Mean angles of kyphosis after 10 years – 41-47%</p> <p>Angle of kyphosis increased in all treatment groups with no significant difference between groups; however, in patients less than 15 years of age with angle of kyphosis >30°, the mean increase by ten years was 30°, compared with 10° in those >15 years (p=0.001)</p> <p><u>Treatment completion rate</u> 11 patients had modification of treatment. 5 in surgery and chemotherapy group (surgery abandoned in two, two required additional surgery and one was given additional chemotherapy) 5 in 6-month chemotherapy group (two given additional chemotherapy, further surgery carried out in three) 1 in 9-month chemotherapy (further surgery)</p>
Source of Funding	Not stated
Additional comments	<ul style="list-style-type: none"> • Period of intake for study was 1975-1978. These 10 year finding were published 20 years later. • Radiographs, sputum, pus and urine samples used to detect active tuberculosis. • Surgery consisted of radical excision of tuberculous focus and repair of resultant gap with autologous bone grafts. • Details of assessment described in previous publication (not available) • Reasons for exclusion from 5 year and 10 year analysis given.

	<ul style="list-style-type: none"> • No intention to treat analysis. • No statistical comparison between characteristics of patients in individual groups. Authors stated that the distributions of the patients were broadly similar in the three groups. • Randomisation method described in previous publication (sealed enveloped) • Investigators did not state whether tests performed blindly or independently. • Not stated whether investigators at different sites used same methodology. • Isoniazid and rifampicin only would not be used in the UK as standard therapy. • Chemotherapy toxicity not discussed.
Citation	
NCC CC ID (Ref Man)	19737 (same population as 19732)

Evidence Table

MGT03: In patients with TB of the spine, is surgery with short course chemotherapy more effective than short course chemotherapy alone in eradicating TB disease?

Bibliographic reference	1978, "Five-year assessments of controlled trials of ambulatory treatment, debridement and anterior spinal fusion in the management of tuberculosis of the spine. Studies in Bulawayo (Rhodesia) and in Hong Kong. Sixth report of the Medical Research Council Working Party on Tuberculosis of the Spine", <i>Journal of Bone & Joint Surgery - British Volume</i> , vol. 60-B, no. 2, pp. 163-177. Ref ID: 158
Study type	Randomised controlled trial
Evidence level	2-
Study objective	To report different management of tuberculosis of the spine Bulawayo (chemotherapy and chemotherapy plus surgery) and Hong Kong (chemotherapy plus surgery)
Number of patients	N =130 randomised (of whom 80 included in this analysis at 5 years) Setting: Bulawayo, Rhodesia (Hong Kong trial also reported in this paper does not address the question).
Patient characteristics	The main criterion for admission to the study was clinical or radiographic evidence of active TB of any vertebral body from the first thoracic to the first sacral inclusive. Patients with lesions involving the cervical spine only were ineligible. Patients were ineligible if they had paralysis severe enough to prevent walking across a room, if they had a history of previous antituberculosis chemotherapy for twelve months or more, or if they had serous extra-spinal disease, tuberculous or not, likely to affect the management of the patient or the response to treatment. <u>Age</u> <15 years: Group 1 – n = 9, Group 2 – n = 6 >15 years Group 1 – n = 36, Group 2 – n = 29 <u>Gender:</u> Male: female Group 1 – 23:22 Group 2 19:16 <u>CNS abnormality:</u> Group 1 n = 6

	<p>Group 2 n = 4</p> <p><u>Total vertebral loss:</u></p> <p><1: Group 1 n = 29 Group 2 n = 23</p> <p>≥1: Group 1 n = 16 Group 2 n = 12</p> <p><u>Number of vertebrae involved</u></p> <p>2 vertebrae – Group 1 n = 31, Group 2 n = 30</p> <p>3 vertebrae – Group 1 n = 11, Group 2 n = 2</p> <p>4 vertebrae – Group 1 n = 3, Group 2 n = 3</p>
Intervention	<p>N=45 Group 1 - Chemotherapy Plus Surgery (open debridement performed within two months of start of chemotherapy). The operation involved removal, as far as possible, of all pus, caseous material, sloughs and sequestra but without removal of unaffected or viable bone except to provide adequate access to the focus. The lesions were widely exposed through trans-thoracic or extra-peritoneal approaches.</p> <p>The following chemotherapy regimens were allocated at random:</p> <p>PH: Isoniazid 6 mg/kg body weight (maximum 300mg) and sodium PAS 0.2g/kg body weight (maximum 10g) given together daily in two doses for eighteen months.</p> <p>SPH: Isoniazid and PAS for eighteen months, as above, plus streptomycin sulphate 20mg/kg body weight (maximum 1.0g) by a single daily intramuscular injection for the first three months.</p>
Comparison	<p>N=35 Group 2 - Chemotherapy Alone. Patients were initially admitted to hospital but were ambulant thereafter. Chemotherapy as in Group 1.</p>
Length of follow-up	<p>5 years</p>
Outcome measures	<p>Status</p> <p>Radiographic activity</p> <p>Changes in vertebral loss and angle of kyphosis</p> <p>Cumulative occurrence of bony fusion</p>
Effect size	<p><u>Status</u> - Favourable status (no sinus or clinically evident abscess, no myelopathy and no modification of allocated regimen, no limitation of physical activity due to spinal lesion and radiologically quiescent disease)</p> <p><u>Chemotherapy and surgery</u></p> <ul style="list-style-type: none"> • In patients undergoing chemotherapy plus surgery 85% had favourable status after 3 years • In patients undergoing chemotherapy plus surgery 84% had favourable status after 5 years <p><u>Chemotherapy alone</u></p>

	<ul style="list-style-type: none"> • In patients undergoing chemotherapy alone 86% had favourable status after 3 years • In patients undergoing chemotherapy alone 83% had favourable status after 5 years <p><u>Radiographic activity</u></p> <ul style="list-style-type: none"> • In patients undergoing chemotherapy plus surgery 95% had no radiographic activity after 5 years • In patients undergoing chemotherapy alone 91% had no radiographic activity after 5 years <p>Changes in vertebral loss</p> <ul style="list-style-type: none"> • In the chemotherapy and surgery group, mean vertebral loss on admission to study was 0.90 vertebral bodies and the mean increase in vertebral loss at 5 years was 0.15 vertebral bodies • In the chemotherapy group, mean vertebral loss on admission to study was 0.67 vertebral bodies and the mean increase in vertebral loss after 5 years was 0.06 vertebral bodies <p>Change in angle of kyphosis</p> <ul style="list-style-type: none"> • In the chemotherapy and surgery group, the mean angle of kyphosis on admission was 28° and the mean increase in angle after 5 years was 11°. • In the chemotherapy group, the mean angle of kyphosis on admission was 24° and the mean increase in angle after 5 years was 6°. <p>No statistical comparison between groups</p> <p>Cumulative occurrence of bony fusion</p> <ul style="list-style-type: none"> • In the chemotherapy and surgery group bony fusion had occurred by 5 years in 82% of patients • In the chemotherapy group bony fusion had occurred by 5 years in 85% of patients <p>No statistical comparison</p>
Source of Funding	Not stated
Additional comments	<ul style="list-style-type: none"> • Study appears to be two separate controlled trials reported in same publication. Baseline characteristics of patients in both trials very different from each other. • Hong Kong trial does not address question as it compares two different types of surgery with chemotherapy. • Some patients received streptomycin in addition to other chemotherapy treatment.

	<ul style="list-style-type: none"> • 50 patients excluded since start of study – reasons given in prior publication. • No statistical tests, confidence intervals or power analysis and small numbers in each group. • No intention to treat analysis. • Adverse effects not discussed in detail. • Isoniazid, PAS and streptomycin would not be used in the UK as standard chemotherapy.
Citation	
NCC CC ID (Ref Man)	19733 (some information from 19735)

Evidence Table	
MGTO4: In patients TB pericarditis on drug treatment, are regimens of six months duration as effective as regimens of longer durations in reducing mortality and morbidity?	
Bibliographic reference	Mayosi BM, Btsekhe M, Volmink JA, Commerford PJ. Interventions for treating tuberculosis pericarditis (Cochrane Review). In: The Cochrane Library, Issue 4, 2003. Chichester, UK: John Wiley & Sons Ltd.
Study type	Cochrane systematic review
Evidence level	1++
Study objective	In people with TB pericarditis, to evaluate the effects on death, life threatening conditions and persistent disability of: 1) 6 month antituberculous drug treatment compared with regimens of 9 months or more 2) corticosteroids 3) pericardial drainage 4) pericardiectomy (in constrictive pericarditis). Only the first objective is relevant to this question.
Number of patients	N/A
Patient characteristics	People of all ages requiring treatment for clinically diagnosed TB pericarditis (effusive, constrictive or effusive-constrictive).
Intervention	6 month antituberculous drug treatment compared with regimens of 9 months or more
Outcome measures	Primary: All cause death Secondary: Death or disabled at 1 to 2 years follow-up. "Disabled" is defined as a history of restricted physical activity, combined with signs of cardiac compromise prespecified in the protocol (such as clinical, radiographic and electrocardiogram evidence of persisting pericardial disease). Death attributed to pericarditis Occurrence of tamponade requiring drainage of the pericardium (pericardiocentesis). Need for excision of the pericardium (pericardiectomy)
Effect size	<ul style="list-style-type: none"> No randomised controlled trials were found that compared antituberculous drug regimens of different durations in tuberculous pericarditis.
Source of funding	Contributors to the fellowship grant for Dr Mayosi: the Medical Research Council, South Africa;

	Medtronic Southern Africa Institute of Cardiovascular Medicine; Cardiac Clinic Research Fund; University of Cape Town, South Africa; and the Nuffield Trust, Oxford, UK.
Additional comments	<ul style="list-style-type: none"> The authors conclude “no trials have assessed antituberculous drug regimens in tuberculous pericarditis. Regimens are therefore based on evidence from trials of pulmonary disease”.
NCC CC ID (Ref Man)	40

Evidence Table	
MGTO5: In patients TB pericarditis are corticosteroids in addition to drug treatment effective in reducing mortality and morbidity?	
Bibliographic reference	Ntsekhe, M., Wiysonge, C., Volmink, J. A., Commerford, P. J., & Mayosi, B. M. 2003, "Adjuvant corticosteroids for tuberculous pericarditis: Promising, but not proven", <i>Qjm: Monthly Journal of the Association of Physicians</i> , vol. 96, no. 8, pp. 593-599.
Study type	Systematic review / meta analysis
Evidence level	1++
Study objective	To determine the effectiveness of adjuvant corticosteroids in tuberculous pericarditis.
Number of patients	Total number of patients in the review = 469 participants Studies included (and country): Hakim, 2000 (N=58, Zimbabwe), Schrire 1959 (N=28, South Africa), Strang 1987 (N=143, South Africa), Strang 1988 (N=240, South Africa).
Patient characteristics	People of all ages requiring treatment for clinically diagnosed TB pericarditis (effusive, constrictive or effusive-constrictive). In the Hakim 2000 study, participants were HIV positive with suspected pericardial effusion. In the Schrire 1959 study participants were on antituberculous chemotherapy for suspected TB pericarditis and no patient characteristics are provided. In the Strang 1987 study, participants had suspected tuberculous constrictive pericarditis and were aged 5 years and older. In the Strang 1988 study participants were aged 5 years or more and were diagnosed as having tuberculous pericardial effusion.
Intervention	Placebo controlled trials comparing the use of corticosteroids with placebo in patients of all ages with a diagnosis of TB pericarditis. Actual study interventions were: Schire 1959: adjuvant cortisone, 300mg loading dose, 100mg/day maintenance dose for several weeks in 14 participants. At a later date, prednisolone 60mg/day with a maintenance dose of 30mg/day was substituted. Strang 1987: adjuvant prednisolone for the first 11 weeks of antituberculous chemotherapy. Adult dose: 60mg/day for first 4 weeks, 30mg/day for weeks 5-8, 15mg Strang 1988: adjuvant prednisolone for the first 11 weeks of antituberculous chemotherapy. Adult dose: 60mg/day for first 4 weeks, 30mg/day for weeks 5-8, 15mg/day for weeks 9-10, 5mg/day for week 11./day for weeks 9-10, 5mg/day for week 11. Hakim 2000: adjuvant prednisolone for the first 6 weeks of antituberculous chemotherapy at a dose of 60mg/day for the first week and taperig by 10mg/day every week.

Comparison	Placebo
Length of follow-up	Unspecified in the Schrire study, 18 months in Hakim's trial and 2 years in the Strang studies.
Outcome measures	All cause death Death or disabled at 1 to 2 years follow-up. "Disabled" is defined as a history of restricted physical activity, combined with signs of cardiac compromise prespecified in the protocol (such as clinical, radiographic and electrocardiogram evidence of persisting pericardial disease). Death attributed to pericarditis Occurrence of tamponade requiring drainage of the pericardium (pericardiocentesis). Need for excision of the pericardium (pericardiectomy). Corticosteroid related adverse events.
Effect size	<ul style="list-style-type: none"> • A combined analysis of patients with effusive and constrictive pericarditis on adjuvant steroids or in a control group (the two studies by Strang) found fewer patients died in the steroids group, however this was not a significant reduction (RR=0.65; 95%CI 0.36 to 1.61). For other outcomes, the group receiving steroids were associated with fewer morbid outcomes, but none were statistically significant (need for repeat pericardiocentesis (RR=0.45; 95%CI 0.20 to 1.05) and need for pericardiectomy (RR=0.85; 95%CI 0.51 to 1.42)). • A combined analysis of the two studies by Strang exploring the effect of steroids on death and persisting pericardial disease at 2 years follow-up, exhibited significant heterogeneity so for this outcome the trials were considered separately. Participants on steroids for pericardial effusion (Strang 1988) were more likely to be cured at 24 months (alive and symptom free) than participants on placebo (RR 0.48; 95%CI 0.29 to 0.8). However, this study had a number of patients lost to follow-up and using sensitivity analysis under the worst case scenario (assuming all of these patients died) statistical significance was lost (RR 0.78; 95% CI 0.52 to 1.18). No difference was found in the trial of participants with suspected constrictive pericarditis (Strang 1987- RR 1.08; 95%CI 0.52 to 1.18). • In the steroid treatments study for HIV positive patients (Hakim 2000) steroids were associated with fewer deaths but this was not statistically significant (RR 0.50; 95%CI 0.15 to 6.63). No difference in the risk of constrictive pericarditis (RR 1.00;95%CI 0.15 to 6.63, p=1) or in the frequency of steroid-related complications was demonstrated.
Source of Funding	MN and CW are recipients of the Don Kennedy Grant and the South African Medical Research Council Africa Fellowship, respectively.
Additional comments	<ul style="list-style-type: none"> • There is a paucity of rigorous evidence in this area as only four small trials were identified. • Loss to follow up was as high as 20% in some of the earlier studies making the findings

	<p>vulnerable to bias (Strang 1987 and 1988)</p> <ul style="list-style-type: none"> • The basis for the diagnosis of tuberculous pericarditis was not given in the Schrire study. In Strang 1987, a definite diagnosis of tuberculosis was made in only 10% of the participants with constrictive pericarditis, and in the pericardial effusion study (Strang 1988), 60% of participants had evidence confirming or supporting a diagnosis of active tuberculosis. The tuberculosis diagnosis was confirmed in 38% of the participants in the Hakim study. • Some of the studies were commenced before echocardiography became widely available, leading to inadequate separation of patients into the different categories of tuberculous pericarditis (effusive, effusive-constrictive and constrictive pericarditis). • The authors suggest that it is possible that steroids may be more effective in the earlier stages of the disease (effusive and effusive-constrictive) with limited effects in the later stages of constriction when fibrosis is established. • The authors note rifampicin induces the hepatic metabolism of steroids, so it is possible that the steroid dose used in the trials to date is too low, and that 120mg of prednisolone rather than 60mg might be more appropriate. • The authors conclude “On the basis of the currently available data, adjuvant prednisolone cannot be recommended for routine use in all patients with tuberculous pericarditis. However it may be reasonable to reserve corticosteroids for critically ill patients with recurrent large effusions who do not respond to pericardial drainage and antituberculous drugs alone. There is a need for large, multi-centre prospective RCTs assessing the effectiveness of adjuvant steroids in tuberculous pericarditis”.
Citation	
NCC CC ID (Ref Man)	19730

Evidence Table	
MGTO5: In patients TB pericarditis are corticosteroids in addition to drug treatment effective in reducing mortality and morbidity?	
Bibliographic reference	Schrire, V. 1959, "Experience with pericarditis at Groote Schuur Hospital, Cape Town: an analysis of one hundred and sixty cases studied over a six-year period", <i>South African Medical Journal</i> , vol. 33, pp. 810-817.
Study type	Quasi-randomised study
Evidence level	1-
Study objective	The study objectives were very general "this study is concerned with the aetiology, natural history and results of treatment, including surgery, in 160 cases of pericarditis". It was not specific to TB or corticosteroids. It did however go on to say later in the report: "an attempt was made to assess whether the administration of corticoids would prevent the development of cardiac constriction".
Number of patients	N=28 Setting: Cape Town, South Africa
Patient characteristics	Participants who were on antituberculous chemotherapy for suspected TB pericarditis. Characteristics were not provided.
Intervention	N=14 While under antituberculous cover, cortisone was prescribed with a loading dose of 300mg and a maintenance dose of 100mg daily for several weeks. At a later date 60mg of prednisolone a day with a maintenance dose of 20mg was substituted.
Comparison	N=14 Control group who were on anti-tuberculous treatment alone (not a placebo group)
Length of follow-up	Not specified
Outcome measures	Constriction requiring pericardiectomy.
Effect size	Of the 14 cases receiving corticoids and antituberculous treatment 4 developed severe constrictive pericarditis requiring surgical interference
Source of Funding	South African Council for Scientific and Industrial Research and the City Council of Cape Town.
Additional comments	<ul style="list-style-type: none"> • Alternate allocation rather than randomisation. • No concealment or mention of blinding. • Small numbers with no power analysis (or statistical tests). • No comparison of baseline characteristics. • Length of follow-up unspecified. • Unclear how the diagnosis was made in these patients. • Unclear how many patients received cortisone and how many prednisolone.

	<ul style="list-style-type: none">The authors concluded that corticoid treatment was ineffective in preventing the development of constriction.
Citation	
NCC CC ID (Ref Man)	19724

Evidence Table	
MGTO5: In patients with TB pericarditis are corticosteroids in addition to drug treatment effective in reducing mortality and morbidity?	
Bibliographic reference	Hakim, J. G., Ternouth, I., Mushangi, E., Siziya, S., Robertson, V., & Malin, A. 2000, "Double blind randomised placebo controlled trial of adjunctive prednisolone in the treatment of effusive tuberculous pericarditis in HIV seropositive patients", <i>Heart</i> , vol. 84, no. 2, pp. 183-188.
Study type	Randomised Controlled Trial
Evidence level	1++
Study objective	To determine the effect of adjunctive prednisolone on morbidity, pericardial fluid resolution and mortality in HIV seropositive patients with effusive TB pericarditis.
Number of patients	N=58 Setting: Two medical school affiliated referral hospitals in Harare, Zimbabwe.
Patient characteristics	Eligibility criteria were age 18-55 years, residence in Harare city to ensure good follow-up, HIV seropositive, no diagnosis of TB within the past two years, large pericardial effusion on echocardiography (more than 1cm anteriorly and > 1cm posteriorly and pericardial aspirate with more than 50% lymphocytes and protein content >30g/l. Exclusion criteria were antituberculous treatment started more than 48 hours before recruitment, corticosteroid treatment within one month, presence of Kaposi's sarcoma or any other malignancy, co-existing life-threatening disease, bacterial pneumonia, pregnancy, cavitating pulmonary TB and other causes of pericardial effusion. The mean age of those in the prednisolone group was 33 years with a mean weight of 57kg and in the placebo group the mean age was 29 years with a mean weight of 54kg. 69% of study participants were male. For most participants their duration of illness was 2 to 8 weeks and the most frequent symptoms were cough and sputum production. 54% had CD4+ counts between 200 and 500 cells/ul. In total 22 (38%) pericardial fluid specimens grew <i>M. tuberculosis</i> . This was 12 in the prednisolone group and 10 in the placebo group.
Intervention	N=29 Prednisolone tablets starting at a dose of 60mg (12 tablets) and tapering by 10mg per week until completion at the end of the sixth week. All patients in both groups received a standard short course anti-tuberculous regimen in accordance with national guidelines. This included rifampicin, isoniazid, pyrazinamide, and ethambutol for two months followed by rifampicin and isoniazid for a further four months in standard doses.
Comparison	N=29 Identical placebo tablets starting at a dose of 60mg (12 tablets) and tapering by 10mg per week until completion at the end of the sixth week.

Length of follow-up	18 months
Outcome measures	The primary end-points were resolution of pericardial effusion and death. The secondary end points were resolution of pre-treatment symptoms and signs, low voltage ECG and corticosteroid related adverse effects. Low voltage of ECG was defined as a QRS complex of <6mm in V5 or V6 and < 4 mm in the limb leads.
Effect size	<ul style="list-style-type: none"> • Three deaths occurred within one week of introduction of antituberculous treatment (one in the prednisolone and two in the placebo group). In the first six months of treatment nine deaths occurred among the 58 patients – one in the prednisolone group and eight in the placebo group. At the end of the study five deaths were recorded in the prednisolone group and 10 in the placebo group. This was a significant difference showing improved survival in the prednisolone group (p=0.004, log rank chi square). • Deaths after six months were all caused by HIV related conditions. Those prior to 6 months were due to disseminated TB but not to constrictive pericarditis. • Improvement in physical activity (p=0.02) and resolution of raised jugular venous pressure (p=0.017), hepatomegaly (p=0.007) and ascites (p=0.051) were faster in prenisolone treated patients compared with those given placebo. Constrictive pericarditis occurred in four patients, two in each group. • There was no difference in the rate of radiologic and echocardiographic resolution of pericardial effusion. • There was no significant difference in the frequency of complications between the two groups. There were three cases of Kaposi's sarcoma but all were in the placebo group.
Source of Funding	CAPS(Pvt) Ltd provided prednisolone and placebo tablets and financial support. The University of Zimbabwe research board provided further funding.
Additional comments	<ul style="list-style-type: none"> • The trial is of high quality although it is small and had no power analysis. • The authors conclude that high dose prednisolone in addition to antituberculous drugs resulted in reduced mortality and quicker improvement of clinical features but did not influence the resolution of pericardial effusion. • It is notable that a systematic review{Ntsekhe, 2003 19730 /id} which includes this study and reports it's results separately (as it is the only study in HIV positive individuals) calculates that steroids were associated with fewer deaths in HIV positive participants but this is not statistically significant (RR=0.5; 95%CI0.19 to 1.28). This is because the relative risk calculated at 18 months does not take into account the timing of the deaths occurring during

	this period.
Citation	
NCC CC ID (Ref Man)	19729

Evidence Table	
MGTO5: In patients TB pericarditis are corticosteroids in addition to drug treatment effective in reducing mortality and morbidity?	
Bibliographic reference	Strang, J. I. G. Management of tuberculous constrictive pericarditis and tuberculous pericardial effusion in Transkei: results at 10 years follow-up. Nunn, A. J., Johnson, D. A., Casbard, A., Gibson, D. G., and Girling, D. J. Qjm: Monthly Journal of the Association of Physicians 97, 525-535. 2004.
Study type	Randomised Controlled Trial
Evidence level	1++
Study objective	Following-up two previous trials by the same author, to see whether the advantages of prednisolone and open drainage were maintained up to 10 years.
Number of patients	N=383 N=143 patients with constrictive pericarditis (N=70 prednisolone, N=73 placebo). N=240 with pericardial effusion (N=118 with effusion not consenting to open drainage with N=57 allocated to prednisolone and N=57 placebo) (N=122 consenting to open drainage with , N=29 allocated to drainage and prednisolone, N=35 drainage and placebo, N=31 no drainage and prednisolone, N=27 no drainage and placebo) Setting: Transkei (East Cape)
Patient characteristics	Patients were from Transkei, of Xhosa ethnic origin, aged 5 years or more, with active non-calcific tuberculous constrictive pericarditis or pericardial effusion. They had received no previous antituberculosis chemotherapy, or no more than 2 weeks of treatment during the previous year. Those consenting to take part were all prescribed the same 6 month standard antituberculosis regimen of streptomycin, isoniazid, rifampicin and pyrazinamide daily for 14 weeks as an inpatient, followed by isoniazid and rifampicin daily up to 6 months. There was evidence of TB in 84% of patients with constriction (this being histological in 40% of those with specimens available) and in 73% of patients with effusion (this being bacterial in 57%). (Examination of pericardial fluid may be considered unnecessary in areas where TB pericarditis is common and when another diagnosis is unlikely). In the constriction group 45% were male with median age 48 (range 5 to 75 years). 6% had unrestricted activity, 47% were out ant about but activity restricted, 23% were confined to home or

	<p>hospital and 24% were bedridden. The great majority had evidence of severe constriction, with tachycardia, low pulse pressure, raised JVP, enlarged liver, ascites and oedema.</p> <p>In the effusion group 43% were male with a median age of 50 (range 6 to 78 years). 8% had unrestricted activity, 34% were out ant about but activity restricted, 20% were confined to home or hospital and 43% were bedridden. Most patients had substantial cardiac embarrassment and 10% had tamponade.</p>
Intervention	<p>N=187 Prednisolone Doses varied by age and treatment week as follows: For those aged 5-9 years Weeks: 1-4: 30mg 5-8: 15mg 9-10: 7.5mg 11: 2.5mg</p> <p>For those aged 10-14 years Weeks: 1-4:45mg 5-8: 22.5mg 9-10: 7.5mg 11: 2.5mg</p> <p>For those aged 15 years or over Weeks: 1-4: 60mg 5-8: 30mg 9-10: 15mg 11: 5mg The tablets were administered under the direct supervision of hospital staff for the firs 11 weeks of treatment.</p>
Comparison	<p>N=196 Matching placebo The tablets were administered under the direct supervision of hospital staff for the firs 11 weeks of treatment.</p>

Length of follow-up	10 years
Outcome measures	<p>Adverse events: Death from pericarditis Pericardiectomy Repeat pericardiocentesis Subsequent open surgical drainage Other: Level of physical activity (1=activity unrestricted, 2=out and about but activity restricted, 3=confined to home or hospital or 4=bedridden).</p>
Effect size	<ul style="list-style-type: none"> • In constriction patients, adverse outcomes occurred in 19/70 (27%) prednisolone vs. 28/73 (38%) placebo but this was not a significant difference (p=0.15). Deaths from pericarditis being 2 (3%) vs. 8 (11%), respectively (p=0.098). • In effusion patients, adverse outcomes occurred in 14/27 (52%) with neither drainage nor prednisolone, vs. 4/29 14% drainage and prednisolone, 4/35 (11%) drainage and placebo and 6/31 (19%) prednisolone and no drainage (p=0.08 for interaction). • In the 122 patients who consented to the open drainage arm, repeat pericardiocentesis was less common in patients who were allocated prednisolone occurring in 4/60 (7%) vs. 11/62 (18%) of those allocated placebo (p=0.06). • In the comparison of prednisolone vs. placebo in patients with effusion, in those who did not receive open drainage adverse outcomes of any type were substantially less frequent in the prednisolone than the placebo group, occurring in 17/88 (19%) compared with 35/88 (40%) respectively (p=0.003). • In effusion patients without open drainage prednisolone reduced the need for repeat pericardiocentesis, which was required in 9 (10%) prednisolone and 20 (23%) placebo patients (p=0.025) • In a multivariate survival analysis (stratified by type of pericarditis), prednisolone reduced the overall death rate after adjusting for age and sex (p=0.044) and substantially reduced the risk of death from pericarditis (p=0.004). At 10 years, the great majority of surviving patients in all treatment groups were either fully active or out and about even if activity was restricted.
Source of Funding	Supported by a grant from the Wellcome Trust
Additional comments	<ul style="list-style-type: none"> • No power analysis and some small groups • Authors note accuracy of diagnosis may be a limitation. • Authors conclude that in the absence of a clear contraindication, a corticosteroid should be

	used in addition to antituberculosis chemotherapy in the management of patients with TB pericarditis.
Citation	
NCC CC ID (Ref Man)	19844