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BRITISH INFECTION SOCIETY GUIDELINES

British Infection Society guidelines for the diagnosis and treatment of tuberculosis of the central nervous system in adults and children

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Summary and key recommendations The aim of these guidelines is to describe a practical but evidence-based approach to the diagnosis and treatment of central nervous system tuberculosis in children and adults. We have presented guidance on tuberculous meningitis (TBM), intra-cerebral tuberculoma without meningitis, and tuberculosis affecting the spinal cord. Our key recommendations are as follows: 1. TBM is a medical emergency. Treatment delay is strongly associated with death and empirical anti-tuberculosis therapy should be started promptly in all patients in whom the diagnosis of TBM is suspected. Do not wait for microbiological or molecular diagnostic confirmation. 2. The diagnosis of TBM is best made with lumbar puncture and examination of the cerebrospinal fluid (CSF). Suspect TBM if there is a CSF

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leucocytosis (predominantly lymphocytes), the CSF protein is raised, and the CSF:plasma glucose is <50%. The diagnostic yield of CSF microscopy and culture for *Mycobacterium tuberculosis* increases with the volume of CSF submitted; repeat the lumbar puncture if the diagnosis remains uncertain. 3. Imaging is essential for the diagnosis of cerebral tuberculoma and tuberculosis involving the spinal cord, although the radiological appearances do not confirm the diagnosis. A tissue diagnosis (by histopathology and mycobacterial culture) should be attempted whenever possible, either by biopsy of the lesion itself, or through diagnostic sampling from extra-neural sites of disease e.g. lung, gastric fluid, lymph nodes, liver, bone marrow. 4. Treatment for all forms of CNS tuberculosis should consist of 4 drugs (isoniazid, rifampicin, pyrazinamide, ethambutol) for 2 months followed by 2 drugs (isoniazid, rifampicin) for at least 10 months. Adjunctive corticosteroids (either dexamethasone or prednisolone) should be given to all patients with TBM, regardless of disease severity. 5. Children with CNS tuberculosis should ideally be managed by a paediatrician with familiarity and expertise in paediatric tuberculosis or otherwise with input from a paediatric infectious diseases unit. The Children's HIV Association of UK and Ireland (CHIVA) provide further guidance on the management of HIV-infected children (www.chiva.org.uk). 6. All patients with suspected or proven tuberculosis should be offered testing for HIV infection. The principles of CNS tuberculosis diagnosis and treatment are the same for HIV infected and uninfected individuals, although HIV infection broadens the differential diagnosis and anti-retroviral treatment complicates management. Tuberculosis in HIV infected patients should be managed either within specialist units by physicians with expertise in both HIV and tuberculosis, or in a combined approach between HIV and tuberculosis experts. The co-administration of anti-retroviral and anti-tuberculosis drugs should follow guidance issued by the British HIV association (www.bhiva.org).
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Introduction

Central nervous system (CNS) tuberculosis occurs in approximately 1% of all patients with active tuberculosis. It results from the haematogenous dissemination of *Mycobacterium tuberculosis* from primary pulmonary infection and the formation of small subpial and subependymal foci (Rich foci) in the brain and spinal cord.[1] In some individuals foci rupture and release bacteria into the subarachnoid space causing meningitis. In others, foci enlarge to form tuberculomas without meningitis.

The timing and frequency of these events in relation to primary pulmonary infection is dependent upon age and immune status. In children, dissemination usually occurs early and the risk of CNS tuberculosis is highest in the first year following infection[1]; in high tuberculosis prevalence countries CNS tuberculosis predominantly effects very young children (<3years). In low tuberculosis prevalence countries such as the UK, most cases are in adults, often immigrants from areas of high tuberculosis prevalence.[2] Immune-suppressed adults, especially those with HIV infection, are more likely to suffer disseminated disease with CNS involvement.[3] Other risk factors include alcoholism, diabetes mellitus, malignancy, corticosteroid treatment, and agents that block the action of tumour necrosis factor.[4]

Methods and evidence-based rating system

The methods used to formulate these guidelines are based on those recommended by the grades of recommendation, assessment, development, and evaluation (GRADE) working group.[5] The writing committee was selected to represent the range of specialists involved with the management of CNS tuberculosis: respiratory physicians, infectious disease physicians, neurologists, clinical microbiologists, HIV physicians, and paediatricians. The committee formulated the guidelines around a series of important clinical questions, and systematically reviewed the published evidence to answer these questions. The published evidence to answer these questions was identified by searches of Medline and PubMed between 1966 and 2008. Personal collections of papers published before 1966 were also included. The main search was performed in February 2008, with a final search of recent literature in September 2008. The search terms used were: 'tuberculous meningitis', 'central nervous system tuberculosis', 'tuberculoma', 'spinal tuberculosis', 'Pott's disease', combined with 'diagnosis', 'imaging' and 'treatment' and 'surgery'. Abstracts and reports from meetings were not included and only papers published in English were reviewed. The quality of each paper was judged according to the GRADE classification.[5] The quality of evidence available to answer almost all the clinical questions was low or very low. A first draft, summarising the available evidence and its quality for each clinical question was prepared for review by the writing group. The group then met to appraise the evidence and formulate specific recommendation for each question. Recommendations were based on the evidence and represent a consensus view from the writing committee. A rating system indicates the strength of each recommendation and the quality of the evidence behind it[5] (Table 1). A final draft was produced with review and agreement from all the group members.

What is the best way of diagnosing CNS tuberculosis?

Do basic clinical and laboratory features help?

Tuberculous meningitis

The diagnosis of TBM in older children and adults is frequently obscured by days to weeks of non-specific

Table 1 Rating system for the strength of the guidelines recommendations and the quality of the evidence.[5]

Strength of the recommendation	Quality of the evidence
A Strongly recommended	I Evidence from randomised controlled trials
B Recommended, but other alternatives may be acceptable	II Evidence from non-randomised studies
C Weakly recommended: seek alternatives	III Expert opinion only
D Never recommended	

symptoms (Table 2),[6–12] such as headache, fever, vomiting, and anorexia. Failure to thrive, loss of weight, irritability, poor appetite, sleep disturbance, vomiting and abdominal pain are often seen in young children.[13] A history of recent tuberculosis contact is common in children (50–90%) as are atypical neurological presentations. Seizures, both febrile and non-febrile, can be the presenting feature in children as can any focal neurological deficit, the commonest being cranial nerve palsies and hemiplegia.[14]

Examination of the cerebrospinal fluid (CSF) is essential and typically reveals a leucocytosis (10–1000 $\times$ 10^3 cells/ml; mostly lymphocytes), raised protein (0.5–3.0 g/l), and CSF:plasma glucose <50% (Table 2). Atypical CSF findings are well described, particularly in immune-suppressed patients, and the CSF can be acellular or contain a predominance of neutrophils.[12,15]

Table 2 The presenting clinical features of tuberculous meningitis in older children and adults as described by recent clinical series.[6,8,11–13]

	Frequency/range
Symptom	
Headache	50–80%
Fever	60–95%
Vomiting	30–60%
Photophobia	5–10%
Anorexia/weight loss	60–80%
Clinical sign	
Neck stiffness	40–80%
Confusion	10–30%
Coma	30–60%
Cranial nerve palsy	30–50%
VI	30–40%
III	5–15%
VII	10–20%
Hemiparesis	10–20%
Paraparesis	5–10%
Seizures – children	50%
Adults	5%
Cerebrospinal fluid	
Clear appearance	80–90%
Opening pressure >25 cm H_20	50%
Leucocyte count ($\times 10^3$/ml)	5–1000
Neutrophils	10–70%
Lymphocytes	30–90%
Protein (g/L)	0.45–3.0[a]
Lactate (mmol/L)	5.0–10.0
CSF glucose:blood glucose < 0.5	95%

[a] Cerebrospinal protein can be >10 g/l in those with spinal block.

Three studies have attempted to define which clinical features are predictive of TBM[16–18] (Table 3). These algorithms emphasise the importance of duration of symptoms and CSF white cells to the diagnosis, but lack validation outside of the centres in which they were generated. The Vietnam algorithm has been re-tested prospectively in Vietnam[19] and in Turkey[20] and found to be sensitive (90–99%) but only moderately specific (80%). Specificity fell to 43% when tested in predominantly HIV infected patients in Malawi,[21] reflecting the inability of the algorithm to differentiate cryptococcal from tuberculous meningitis.

Cerebral tuberculomas without meningitis

The clinical features of cerebral tuberculoma without meningitis are dependent on their anatomical location,[22] but are often asymptomatic.[23] Constitutional symptoms vary, but most patients complain of headache, fever, and weight loss.[24] Seizures – both focal and generalised – are the commonest presenting feature in both adults and children.[25] Focal neurological signs are much less common, but motor and cerebellar abnormalities and papilloedema are the most frequently reported in adults.[25] Unusual manifestations include hypopituitarism, chorea, and brain-stem syndromes.[22,26–28] Examination of the CSF reveals an elevated total protein in most patients and a pleocytosis of 10–100 cells/mm^3 in 50%.[29] Tuberculomas cannot be distinguished from other cerebral space-occupying lesions by clinical features alone.

Spinal tuberculosis

Tuberculosis can affect any part of the spinal cord, including the nerve roots, and therefore can present with upper or lower motor neuron involvement, or a mixed clinical picture.[30,31] Around 10% of cases with TBM have some form of spinal tuberculosis. Vertebral body tuberculosis (Pott's disease) with cord impingement accounts for the majority of all cases with spinal involvement and most commonly presents with pain, a gibbus, and signs of extrinsic cord compression. Extra-dural cord tuberculomas cause more than 60% of cases of non-osseous paraparesis, although tuberculomas can occur in any part of the cord.[32] Tuberculous radiculomyelitis is a rare but well-reported disease, characterised by subacute paraparesis, radicular pain, and bladder dysfunction.[33,34] Syringomyelia is a rare complication of spinal tuberculosis.[35]

Recommendation

Clinical features can help distinguish TBM from other causes of meningitis, but are of little help in the specific diagnosis of tuberculoma or spinal tuberculosis (A,II). Diagnostic algorithms (Table 3) *can help identify adults and older children with TBM, although they should not be used in those infected with HIV. We recommend the aids are used to identify the highest risk patients in whom every effort should be made to make a microbiological diagnosis and in whom empiric anti-tuberculosis therapy should be strongly considered (B,II)* (Fig. 1).

Table 3 Published diagnostic rules for the diagnosis of tuberculous meningitis.

Age group	Presenting clinical features predictive of TBM	Suggested use and performance
Children rule (1 month to 12 years)[16]	More than 6 days of symptoms Optic atrophy Abnormal movements Focal neurological deficit Neutrophils forming less than half the total numbers of CSF leucocytes	$\geq$1 variable present (98% sensitive, 44% specific) $\geq$2 variables present (77% sensitive, 57% specific) $\geq$3 variables present (55% sensitive, 98% specific)
Children and adults rule (5 months to 56 years)[18]	Duration of symptoms greater than 5 days Clear CSF CSF white cell count $< 1000 \times 10^3$/ml Lymphocytes >30% of total number of CSF white cells CSF protein >100 mg/dl	$\geq$2 variables present (93% sensitive and 77% specific)
Adult rule (>15 years)[17]	Age $\geq$ 36 years (score +2) or < 36 (score 0) Blood WCC (10^3/ml) $\geq$15000 (score +4) or <15000 (score 0) History of illness $\geq$ 6 days (score −5) or < 6 days (score 0) CSF total WCC (10^3/ml) $\geq$ 750 (score +3) or < 750 (score 0) CSF neutrophils $\geq$ 90% (score +4) or < 90% (score 0)	Total score $\leq +4$ = TBM Total score $> +4$ = bacterial meningitis (90—99% sensitive, 79—82% specific)

Is conventional microbiology useful?

Tuberculous meningitis

The search for acid-fast bacilli (AFB) in CSF is crucial for the rapid diagnosis of TBM and the older literature suggest that they can be seen in up to 80% of adult cases,[36,37] but only 15—20% of children. Positive CSF smear and culture is independently associated with large volumes (>6 ml) of CSF submitted for examination[38]; repeated lumbar punctures and CSF examination also increase diagnostic yield.[36,37] *M. tuberculosis* has been isolated from significantly smaller CSF volumes from HIV infected than uninfected individuals.[38] There are very few data defining the maximum safe volume of CSF removed at lumbar puncture, especially in children. CSF volume and production rate increase with age and weight[39—41] as does the volume of CSF that can be safely taken at lumbar puncture (Table 4). Liquid culture media may recover more bacteria from CSF than solid media[42] and is more sensitive than CSF microscopy for AFB, but is too slow (>2 weeks to positive result) to help treatment decisions.

Tuberculoma without meningitis and spinal tuberculosis

AFB are less commonly found in the CSF of patients with cerebral tuberculoma or spinal tuberculosis compared to those with TBM[43] and tissue examination is usually required to confirm the diagnosis. Stereotactic techniques have improved the safety of brain biopsy: Indian investigators reported stereotactic biopsy was diagnostic in 75/80 (94%) patients and only 1 patient suffered complications.[44] Immunohistochemical detection of *M. tuberculosis* antigens in tissue has been reported by Indian researchers to be more sensitive than bacteriology or PCR.[45]

Recommendation

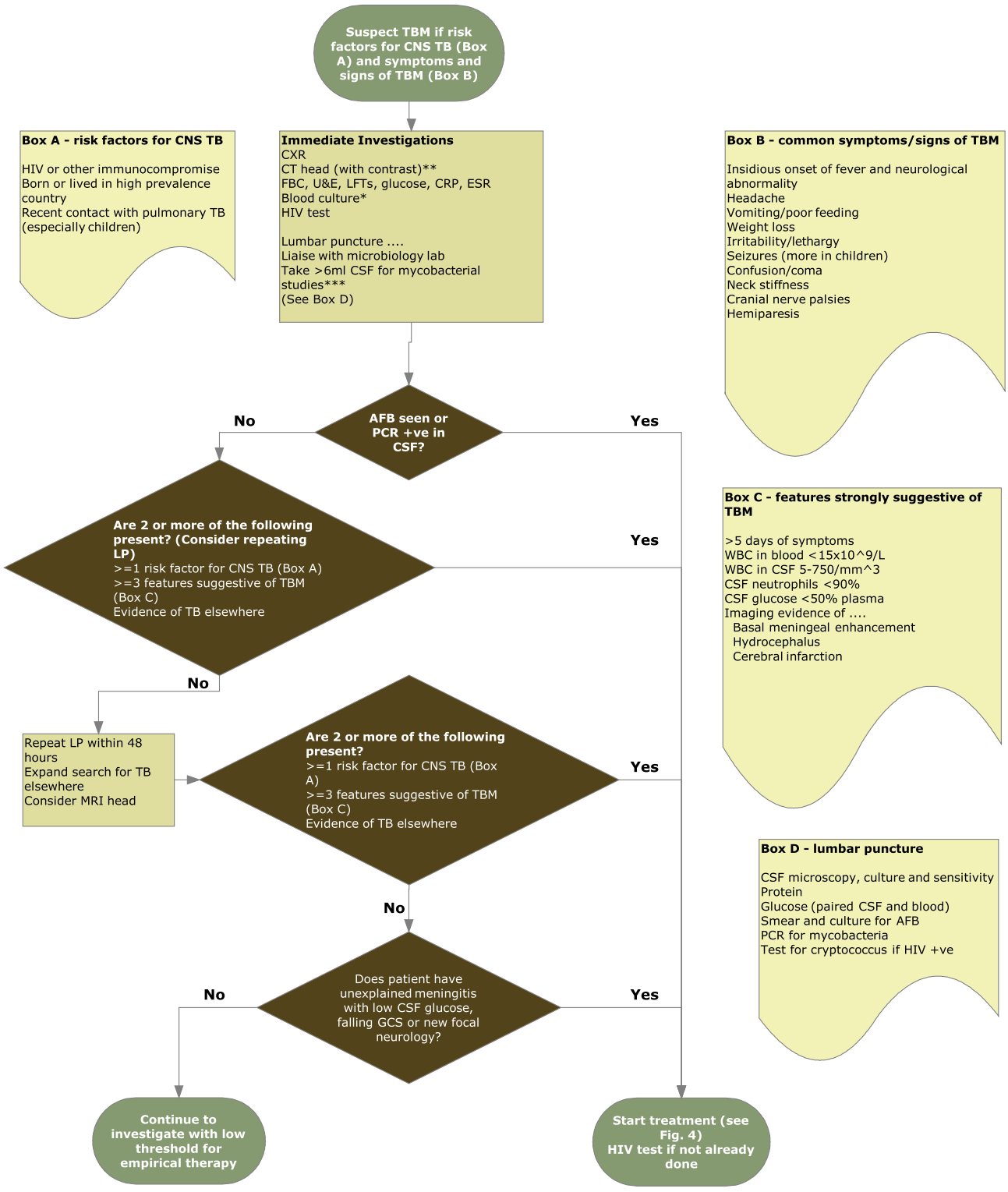
The search for AFB in CSF and tissue remains the best rapid diagnostic test for CNS tuberculosis (Fig. 1) *(A,II). Bacteria may be seen in the CSF of up to 80% of adult patients with TBM, although the diagnostic yield is critically dependent upon the volume of CSF submitted and the care with which it is examined (see panel 1). At any age, approximately 10% of total CSF volume can be taken for examination* (Table 4)*: when TBM is suspected in adults at least 6 ml of CSF should be taken exclusively for mycobacterial studies (A,II). Repeated CSF examinations are strongly encouraged, particularly if the diagnosis of TBM is suspected (B,II). Once anti-tuberculosis medication is commenced, the sensitivity of smear and culture falls rapidly. The deposit should be stained and cultured on solid or in liquid media; an aliquot of deposit may be taken for nucleic acid amplification if required (B,II). Culture is too slow to help in initial treatment decisions, but may provide critical drug susceptibility information once treatment has started.*

A tissue biopsy has much higher diagnostic yield than CSF for the diagnosis of tuberculoma and spinal tuberculosis (A,II) (Figs. 2 and 3)*. A careful search should be made for extra-neural disease that may be biopsied safely (A,II). Further imaging with ultrasound, MRI and computerised tomography (CT) of abdomen, pelvis and chest may reveal evidence of tuberculosis not detected by plain radiography. Gastric aspirates and bone marrow aspirates may assist in detecting extra-neural tuberculosis in children (B,II). Stereotactic brain biopsy should be considered for the diagnosis of tuberculoma if other investigations fail to confirm active extra-neural tuberculosis (A,II).*

Are nucleic acid amplification techniques useful?

Tuberculous meningitis

Recent meta-analysis calculated that commercial nucleic acid amplification (NAA) assays for the diagnosis of TBM were 56% sensitive (95% CI 46—66%) and 98% specific (95% CI 97—99%).[46] Most studies conclude that commercial NAA tests



Notes

*** Conventional aerobic and anaerobic blood cultures. Mycobacterial blood cultures only recommended for immunocompromised patients (for example, those with advanced HIV infection).**

**** CT head can be performed after the LP if there are no clinical contra-indications to an immediate LP.**

***** CSF volumes should be adjusted according to the age of the patient - see Table 4.**

Figure 1 Diagnosis of TB meningitis in adults and children.

Table 4 Estimates of CSF production rate, total CSF volume and the safe recommended CSF volume taken at lumbar puncture for different age groups.[39–41]

	Mean CSF production rate (ml/h)	CSF volume (mls)	Safe CSF volume to take at LP (mls)
Adult	22	150–170	15–17
Adolescent	18	120–170	12–17
Young child	12	100–150	10–15
Infant	10	60–90	6–9
Term Neonate	1	20–40	2–4

can confirm cerebral tuberculosis, but cannot rule it out.[47] Comparisons of NAA, microscopy and culture using large volumes of CSF have indicated that the sensitivity of microscopy was similar to NAA for the diagnosis of TBM[48] and repeated testing gave the highest diagnostic yield.[49] The sensitivity of CSF microscopy and culture falls rapidly after the start of treatment, whereas mycobacterial DNA may remain detectable within the CSF until one month after the start of treatment.[48,50] Preliminary studies have suggested quantitative real time polymerase chain reaction (PCR) may enhance bacterial detection in the CSF[51] and might be a useful future tool in assessing treatment response.[52]

Recommendation

We recommend performing a commercial NAA assay on CSF for all forms of suspected CNS tuberculosis (A,II), although a negative test does not rule out tuberculosis. The diagnostic yield of NAA increases when large volumes of CSF are processed. NAA tests are more useful than conventional bacteriology after the start of anti-tuberculosis treatment. NAA assays that detect the rifampicin resistance genotypes should be requested when the risk of drug resistant tuberculosis is high (A,II) (see Fig. 4).

Are other assays – the tuberculin skin test, CSF adenosine deaminase, interferon-gamma release assays – helpful?

Tuberculin skin testing

The performance of the tuberculin skin test for the diagnosis of tuberculosis varies according to age, vaccination with BCG, nutritional status, HIV infection, and technique of administration.[53] The diagnostic utility of skin testing for CNS tuberculosis is highly variable: in some studies only 10–20% of patients with CNS tuberculosis have a positive test[6,54]; others report around 50% are positive.[55] Rates for children vary between 30 and 65%,[14,56–58] although individuals from high tuberculosis prevalence areas are more likely to have positive tests with an unrelated illness.[54]

CSF adenosine deaminase activity

The activity of adenosine deaminase (ADA) is raised in the CSF of patients with TBM and has been evaluated as a diagnostic assay.[59–71] Lack of specificity has been the major problem: high CSF ADA activity has been reported from patients with lymphomas, malaria, brucellosis and pyogenic meningitides. A recent study in HIV infected adults reported a diagnostic sensitivity of 57% with false positive tests observed in cerebral CMV infection, cryptococcal meningitis, and cerebral lymphomas.[68]

Interferon-gamma release assays (IGRA)

Recent studies suggests two new commercial assays (QuantiFERON-TB gold and T-SPOT.*TB*), based on the detection of interferon-gamma from lymphocytes in response to *M. tuberculosis* specific antigens, are more accurate than skin testing at diagnosing latent tuberculosis.[72] Whether these assays can be adapted to diagnose active tuberculosis is uncertain.[73] The detection of interferon-gamma-producing T-cells in bronchial-alveolar lavage fluid has been used successfully to diagnose pulmonary tuberculosis[74] and case reports suggest similar assays may be useful in the diagnosis of TBM.[75,76] However, others have found that CSF lymphocytes die rapidly when stimulated with *M. tuberculosis* specific antigens ex vivo and the test fails.[77] The same investigators reported that 50% of patients with culture-confirmed TBM had no detectable *M. tuberculosis*-specific interferon-gamma producing lymphocytes in peripheral blood at presentation.[78]

Recommendation

CSF adenosine deaminase activity is not recommended as a routine diagnostic test for CNS tuberculosis (B,II). The tuberculin skin test and IGRAs (using peripheral blood) may provide indication of previous tuberculosis infection and are probably most useful in young children, but results need to be interpreted cautiously as neither is sufficiently sensitive nor specific to diagnose active disease. Currently, IGRAs are only licensed for the diagnosis of latent tuberculosis and cannot be recommended for the diagnosis of active CNS disease (B,II).

What is the role of imaging investigations?

Tuberculous meningitis

About 50% of patients with TBM have chest X-rays suggesting active or previous pulmonary tuberculosis[12]; 10% have miliary disease, which strongly suggests CNS involvement. Chest CT may reveal abnormalities missed by conventional X-ray: evidence of pulmonary tuberculosis was found in 36/74 Turkish patients with TBM in whom chest X-ray was considered normal.[79]

The commonest cerebral CT features of TBM are hydrocephalus and basal contrast enhancing exudates.[80] Both features are more common in children (~80%) than adults (~40%)[80] and may be absent in the elderly with TBM.[81] Infarctions as a result of ongoing vasculitis or tuberculoma are found in approximately 20% of patients at presentation.[80,82,83] More than 70% develop tuberculoma during treatment, although the majority are asymptomatic.[23] Infarctions most commonly involve the basal ganglia and the territories of the medial striate and thalamoperforating arteries.[23,84]

South African investigators reported that the combination of hydrocephalus, basal enhancement and infarction was

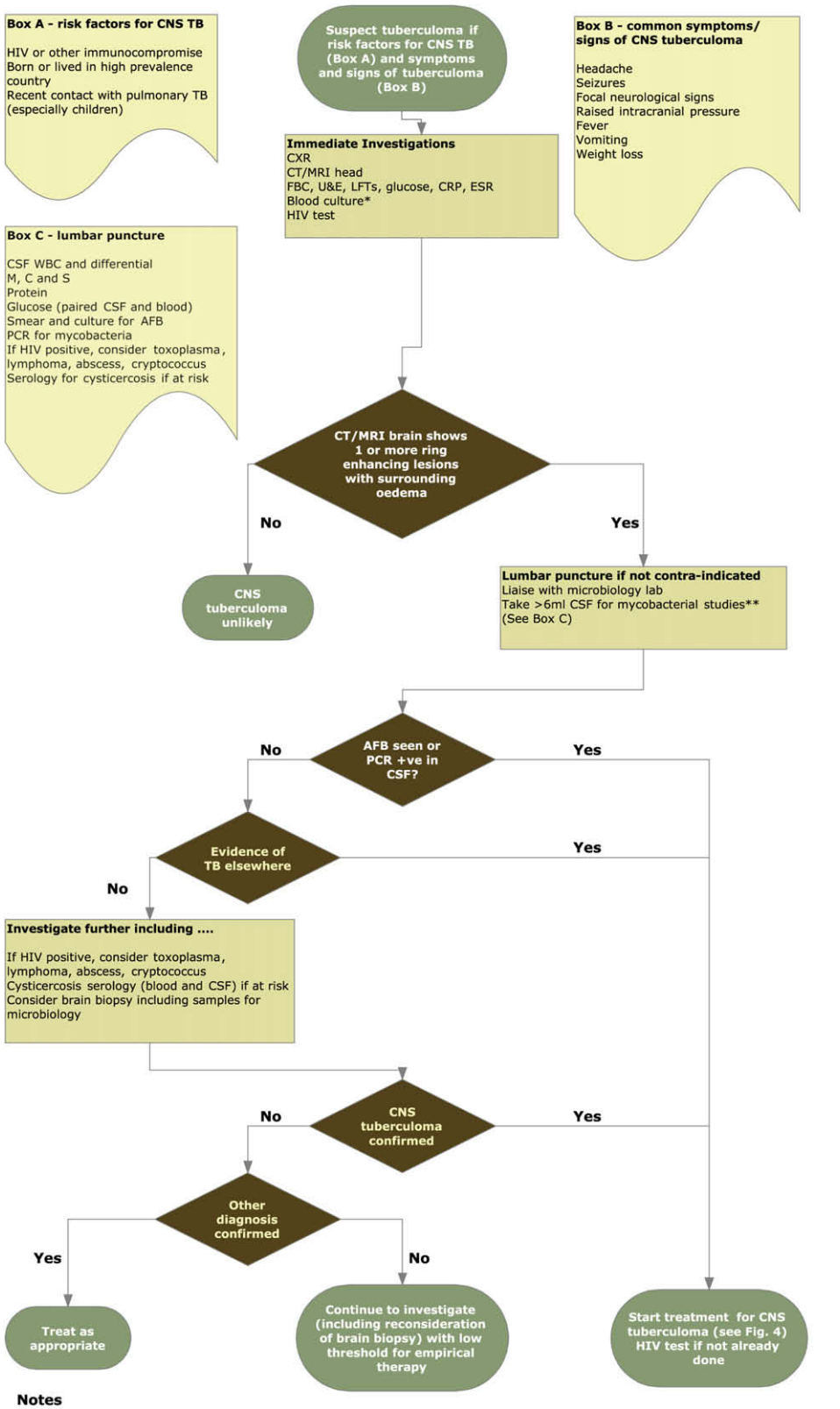
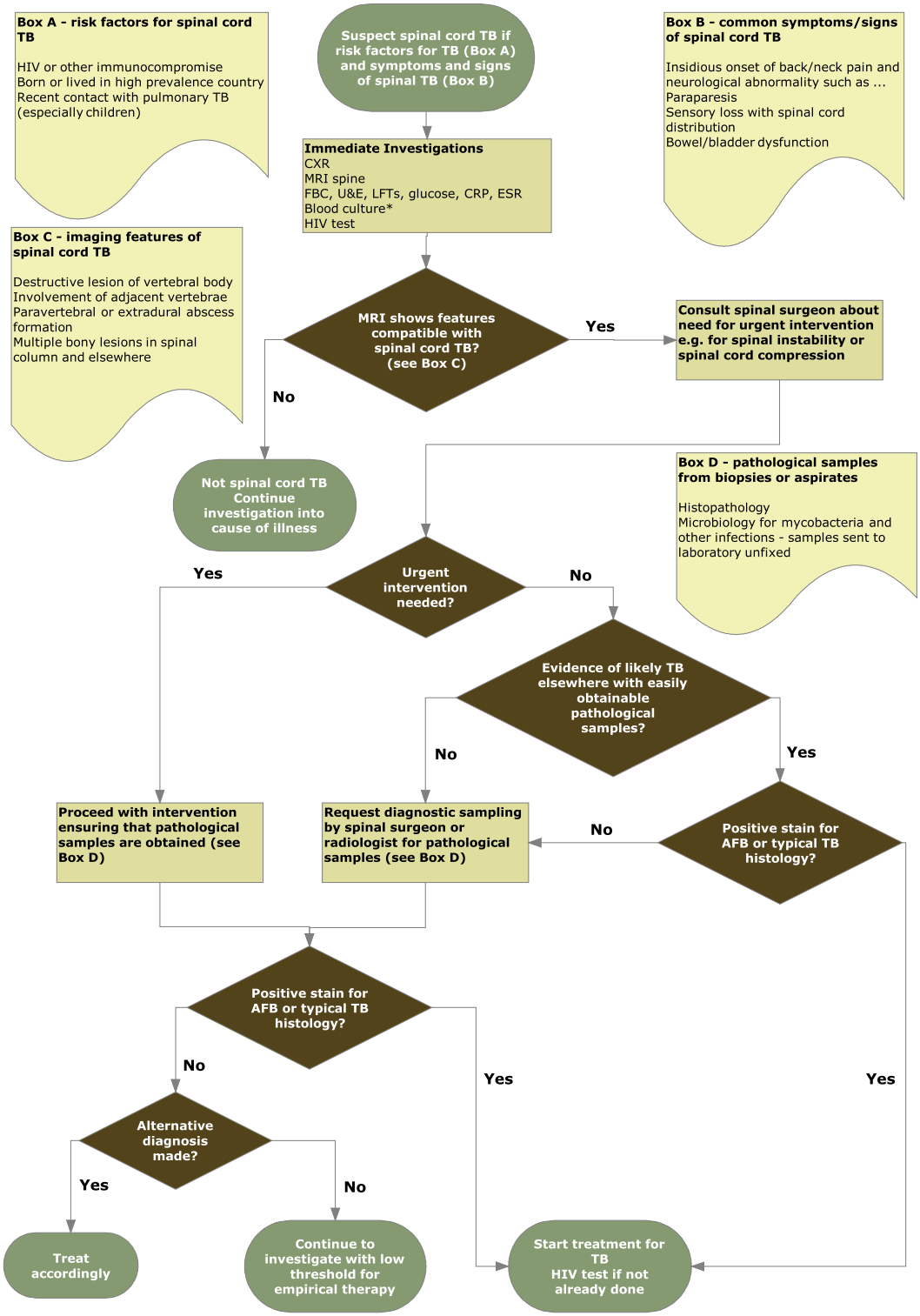


Figure 2 Diagnosis of CNS tuberculoma in adults and children.



Notes

*** Conventional aerobic and anaerobic blood cultures. Mycobacterial blood cultures only recommended for immunocompromised patients (for example, those with advanced HIV infection).**

Figure 3 Diagnosis of spinal cord TB in adults and children.

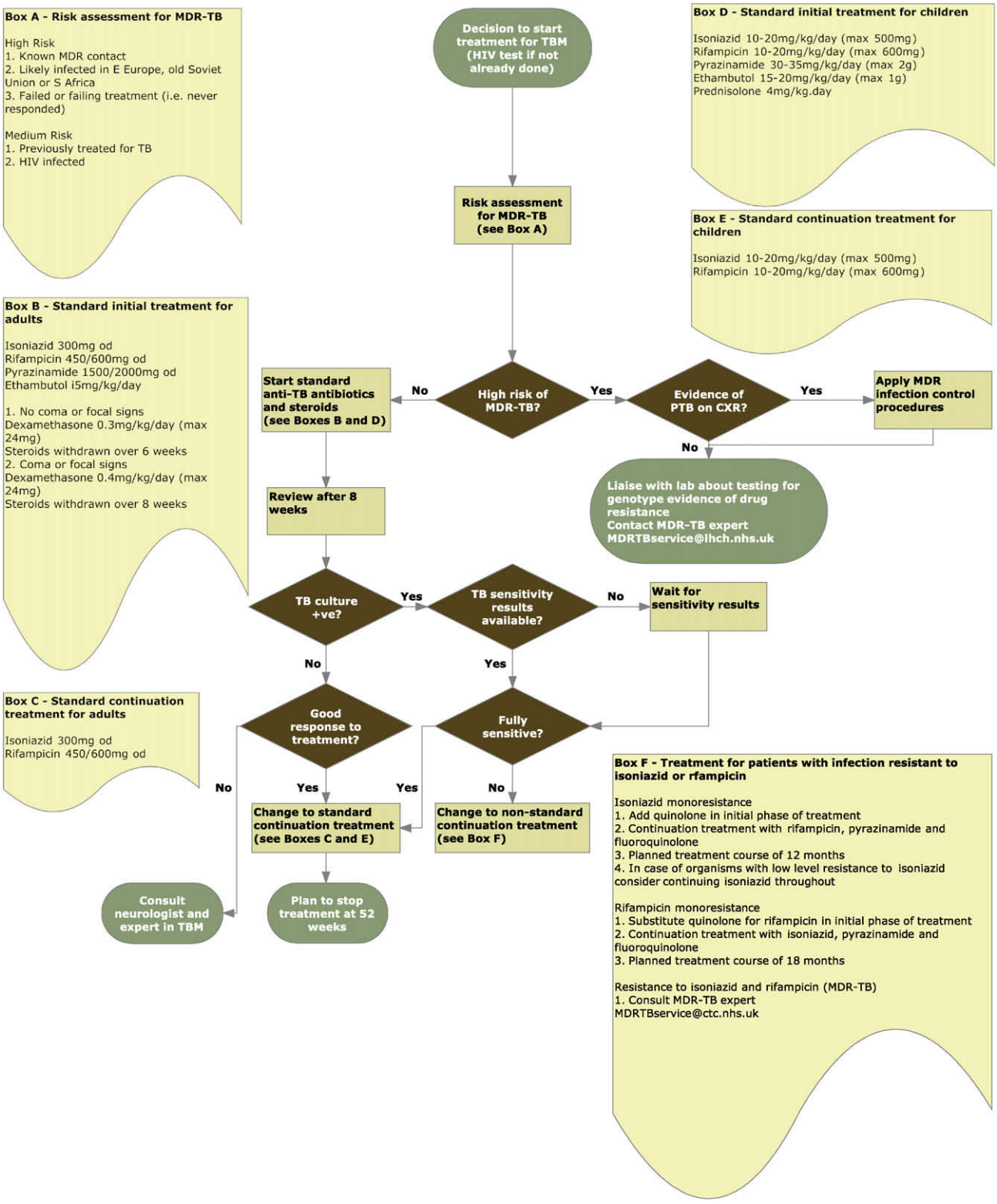


Figure 4 Management of TB meningitis in children and adults.

100% specific and 41% sensitive for the diagnosis of childhood TBM, although the authors suggested pre-contrast hyperdensity in the basal cisterns was the best predictor of TBM.[85]

Magnetic resonance imaging (MRI) provides high definition of infra-tentorial lesions and the early cerebral changes of TBM,[86,87] but data regarding the diagnostic sensitivity and specificity of these features are limited. Cryptococcal meningitis, cytomegalovirus encephalitis, toxoplasmosis, sarcoidosis, meningeal metastases, and lymphoma may all produce similar radiographic findings.[88]

Cerebral tuberculoma without meningitis

CT and MRI demonstrate the typical features of contrast enhancing ring lesions with surrounding oedema; the latter being better able to demonstrate small lesions and those in the posterior fossa and brain stem.[89] Increased use of MRI has shown that infra-tentorial tuberculomas are more common than previously thought.[90,91] Neither of these imaging modalities is able to reliably distinguish tuberculoma from other causes of ring enhancing lesions, in particular pyogenic bacterial abscess, neurocysticercosis (unless MRI reveals a parasitic scolex within the lesion), toxoplasmosis, or neoplasia.[92]

Advances in magnetic resonance spectroscopy (MRS) have shown most promise in differentiating the causes of ring enhancing brain lesions: a large lipid CH_2 peak has been used to specifically identify tuberculomas[93]; others have suggested tuberculomas can be distinguished from neurocysticercosis on the basis of choline/creatine ratio >1 in tuberculoma.[94]

Spinal tuberculosis

The MRI characteristics of vertebral body tuberculosis have been extensively reported.[95] The thoracic spine is most commonly affected; the radiological features include bone marrow oedema and enhancement, posterior element involvement, canal stenosis, and spinal cord or nerve root compression.[96] Inter-vertebral disc enhancement, vertebral collapse and kyphosis deformity are particularly suggestive of tuberculosis,[97] but radiological investigations cannot accurately distinguish tuberculosis from pyogenic bacterial infections, fungal infections, and neoplasia.[95] Vertebral intra-osseous abscess, disc abscess, abnormal para-spinal signal intensity, and involvement of multiple vertebral bodies are common in tuberculosis but rare in pyogenic bacterial disease.[98,99] Brucellar spondylitis cannot be distinguished radiologically from tuberculosis.[100]

The imaging characteristics of cord tuberculosis are less well described. Small case series suggest $>90\%$ of patients with intra-medullary cord tuberculosis have an extra-neural focus of disease.[31,101] Typical MRI findings include fusiform swelling of the cord with ill-defined iso- to hyper- intense lesions with rim enhancement indicating granulomatous inflammation.[101]

Tuberculous radiculomyelitis involves more than one spinal region in $>80\%$, with the thoracic and cervical region being most commonly affected.[102,103] The CSF usually shows increased signal intensity on T1-weighted images, which may be associated with complete loss of the cord-CSF interface and an irregular cord outline. Subarachnoid nodules, clumping of the cauda equine nerve roots, and CSF loculations may also be seen. Contrast enhancement may be seen in the meninges (80%), cord (20%), and nerve roots (30%).[102,103]

Recommendation

The brain of every patient with TBM should be imaged with contrast enhanced CT either before the start of treatment (as part of the diagnostic work-up), or within the first 48 h of treatment (A,II) (Fig. 1). *Early brain CT can help diagnose TBM, and will provide important baseline information particularly when considering surgical interventions for hydrocephalus.*

All patients with suspected cerebral tuberculoma or spinal cord tuberculosis should be investigated by MRI (A,II) (Figs. 2 and 3) *as it is critical to demonstrate whether surgery is indicated and to follow the subsequent response to therapy (A,II). It is rarely possible diagnose tuberculosis on the basis of imaging alone. An extra-neural focus of tuberculosis should be sought clinically and radiologically in all patients with CNS tuberculosis as it may indicate safer and more accessible sites for diagnostic sampling. All patients should have a chest-X-ray as part of the diagnostic assessment (A,II).*

How should CNS tuberculosis be treated?

What is the best anti-tuberculosis drug regimen?

Chemotherapy for CNS tuberculosis follows the model of short course chemotherapy for pulmonary tuberculosis — an intensive phase of treatment, followed by a continuation phase. But unlike pulmonary tuberculosis, the optimal drug regimen and duration of each phase are not clearly established. Isoniazid and rifampicin are the key components of the regimen. Isoniazid penetrates the CSF freely[104,105] and has potent early bactericidal activity.[106] Rifampicin penetrates the CSF less well (maximum concentrations around 30% of plasma), but the high mortality from rifampicin resistant TBM has confirmed its central role in the treatment of CNS disease.[107] There is no conclusive evidence to demonstrate that pyrazinamide improves outcome of CNS tuberculosis, although it is well absorbed orally and achieves high concentrations in the CSF.[108,109] Isonaizid, rifampicin and pyrazinamide are considered mandatory at the beginning of TBM treatment[110] and some centres use all three drugs for the duration of therapy.[111]

There are no data from controlled trials to guide choice of the fourth drug. Most authorities recommend either streptomycin or ethambutol, although neither penetrates the CSF well in the absence of inflammation,[104,112,113] and both can produce significant adverse reactions. Streptomycin should not be given to those who are pregnant or have renal impairment and resistance is relatively common worldwide.[114] Ethambutol-induced optic neuropathy is a concern, especially when treating comatose patients, although at the standard dose of 15—20 mg/kg the incidence is less than 3%.[115] Some centres, notably in South Africa, advocate ethionamide, which penetrates healthy and inflamed meninges[116] but it can cause severe nausea. Prothionamide may be better tolerated. The fluoroquinolones may represent an effective fourth agent, although data concerning their CSF pharmacokinetics and safety during prolonged therapy are limited.[117–119] Fluoroquinolones should be avoided in women who are pregnant or breastfeeding and prolonged fluoroquinolone therapy is not advised for children.[120]

The doses of anti-tuberculosis drugs for the treatment of CNS tuberculosis have conventionally followed those used for pulmonary tuberculosis, although this approach has been questioned.[58] Some have suggested >5 mg/kg isoniazid for the treatment of adult TBM[110] and there is considerable experience of higher doses (10—20 mg/kg to a maximum of 500 mg) in children.[58] At standard doses isoniazid achieves CSF levels 10—15 times the minimum

inhibitory concentration of susceptible *M. tuberculosis*,[105] and there are no data to suggest higher doses improve outcome or shortens treatment in adults. Rifampicin penetrates the CNS less well than isoniazid[104] and high doses (20 mg/kg to a maximum of 600 mg) are reported to be well tolerated in children[58] and may increase the early bacterial kill.[121] Pyrazinamide crosses the blood–brain barrier well, and in children has been used at doses of 40 mg/kg to a maximum of 2 g.[58] Once through the intensive phase of treatment, doses can be reduced to standard levels.[58] The increased risk of adverse events with higher doses of anti-tuberculosis drugs must be consideration for, unlike the treatment of pulmonary tuberculosis, interruptions in treatment are an independent risk factor for death from TBM.[111]

A systematic review and meta-analysis concluded that six months of treatment were probably sufficient for TBM, provided the likelihood of drug resistance was low.[122] However, most authorities recommend 12 months treatment,[123,124] prompted by the uncertain influences of disease severity, CNS drug penetration, undetected drug resistance and patient compliance on response to therapy.

Recommendation

The recommended first-line treatment regimen for all forms of CNS tuberculosis is given in Table 5 *and* Fig. 4 *(A,II). Drugs should be taken each day either individually or in combination form (B,II). Patients should be treated for a minimum of 12 months (A,II).*

Do adjunctive corticosteroids improve outcome?

Tuberculous meningitis

Adjunctive corticosteroid treatment of TBM has been recommended for more than 50 years, but there has been long-standing concern that corticosteroids reduce the penetration of anti-tuberculosis drugs into the CNS, cause gastro-intestinal bleeding, and might save lives but increase the number of disabled survivors. These concerns have remained unsubstantiated.[105,111,125] A recent Cochrane systematic review and meta-analysis of 7 randomised controlled trials involving 1140 participants (with 411 deaths) concluded that corticosteroids improved outcome in HIV-negative children and adults with TBM, but the benefit in HIV infected individuals remains uncertain.[125] The results were heavily influenced by a study performed in 545 Vietnamese adults (199 deaths),[111] which observed that dexamethasone treatment was associated with a significantly reduced risk of death (relative risk, 0.69; 95% CI 0.52–0.92), but was not associated with a significant reduction in the proportion either dead or severely disabled by 9 months of treatment. The effect on survival was consistent across all grades of disease severity. The study included 98 HIV-infected patients: dexamethasone was associated with a non-significant reduction in death and death or severe disability in these patients (stratified relative risk, 0.78; 95% CI 0.59–1.04).

There are no data from controlled trials comparing different corticosteroid regimens; therefore choice of regimen should be based on those found to be effective in the published trials (Table 6).

Tuberculoma without meningitis and spinal tuberculosis

No published controlled trials have examined whether patients with intra-cranial tuberculomas without meningitis or spinal cord tuberculosis benefit from adjunctive corticosteroids, although they are widely advocated.[31,126,127] Anecdotally, they improve symptom and seizure control and reduce tuberculoma size and peri-lesional oedema.[126] Duration of therapy varies depending on response; it is common for symptoms to return once the dose is reduced. There are case reports describing successful treatment of cerebral tuberculomas with thalidomide.[128–130] However, a randomised controlled trial of thalidomide for the treatment of TBM in children was stopped early because of increased adverse events in the thalidomide arm.[131]

Recommendation

We recommend that all patients with TBM receive adjunctive corticosteroids regardless of disease severity at presentation (A,I) (Fig. 4). *The regimen should follow those used in recent controlled trials* (Table 6) *(A,II). Adults (>14 years) should start treatment with dexamethasone 0.4 mg/kg/24 h with a reducing course over 6–8 weeks. Children (≤14 years) should be given prednisolone 4 mg/kg/24 h (or equivalent dose dexamethasone: 0.6 mg/kg/24 h) for 4 weeks, followed by a reducing course over 4 weeks (A,I).*

There is insufficient evidence to recommend routine adjunctive corticosteroids for all patients with tuberculomas without meningitis, or with spinal cord tuberculosis. However, they may be helpful in those patients whose symptoms are not controlled, or are worsening, on anti-tuberculosis therapy, or who have acute spinal cord compression secondary to vertebral tuberculosis (B,II). Similar doses to those used for TBM should be

Table 5 Recommended treatment regimen for CNS tuberculosis caused by fully susceptible *M. tuberculosis*.

Drug	Daily dose		Route	Duration
	Children	Adults		
Isoniazid	10–20 mg/kg (max 500 mg)	300 mg	Oral	12 Months
Rifampicin	10–20 mg/kg (max 600 mg)	450 mg (<50 kg) 600 mg (≥50 kg)	Oral	12 Months
Pyrazinamide	30–35 mg/kg (max 2 g)	1.5 g (<50 kg) 2.0 g (≥50 kg)	Oral	2 Months
Ethambutol	15–20 mg/kg (max 1 g)	15 mg/kg	Oral	2 Months

Table 6 Corticosteroid regimens used in controlled trials associated with significant improvements in outcome.

Trial	Girgis et al.[193]	Schoeman et al.[194]	Thwaites et al.[111]	
Age of subjects	60% <14 years (median 8 years)	<14 years	>14 years	
MRC Grade	All grades	Grade II and III	Grade I	Grade II and III
Drug	Dexamethasone	Prednisolone	Dexamethasone	Dexamethasone
Time	Dose/route	Dose/route	Dose/route	Dose/route
Week 1	12 mg/day im (8 mg/day if <25 kg)	4 mg/kg/day[b]	0.3 mg/kg/day iv	0.4 mg/kg/day iv
Week 2	12 mg/day im (8 mg/day if <25 kg)	4 mg/kg/day	0.2 mg/kg/day iv	0.3 mg/kg/day iv
Week 3	12 mg/day im(8 mg/day if < 25 kg)	4 mg/kg/day	0.1 mg/kg/day oral	0.2 mg/kg/day iv
Week 4	Reducing over 3 weeks to stop[a]	4 mg/kg/day	3 mg total/day oral	0.1 mg/kg/day iv
Week 5		Reducing dose to stop[c]	Reducing by 1 mg each week over 2 weeks	4 mg total/day oral
Week 6				Reducing by 1 mg each week over 3 weeks

[a] Dexamethasone tapered to stop over 3 weeks: exact regimen not published.
[b] Route of administration not published.
[c] Prednisolone tapered to stop over unspecified time: regimen not published.

given (B,III). Thalidomide should not be used for the routine treatment of TBM (A,I), but may be helpful in patients with tuberculomas that are not responding to anti-tuberculosis drugs and high dose corticosteroids (B,II).

When are surgical interventions indicated?

Hydrocephalus is the commonest reason for neurosurgical referral in patients with TBM, but only one randomised controlled trial has been published examining the management of this problem. 57 Children with communicating hydrocephalus were given anti-tuberculosis drugs and randomly allocated to intra-thecal hyaluronidase, or oral acetazolamide and frusemide, or no intervention.[132] Intra-cranial pressure reduced significantly faster in the acetazolamide and frusemide group, although no effect on survival or disability was observed.

Most authorities suggest early ventriculo-peritoneal shunting should be considered in all patients with non-communicating hydrocephalus,[133,134] although outcomes are variable.[135–137] Response to external ventricular drainage has failed to predict those who benefit from early shunting.[133] Endoscopic third ventriculostomy is advocated by some centres as an alternative to shunt surgery.[138,139,140]

Rarely, tuberculomas coalesce and liquefy to cause tuberculous cerebral abscess which may necessitate surgery.[141,142] There are various treatment options, including aspiration, repeated aspiration through a burr hole, stereotactic aspiration and total excision, but there is no consensus as to which is best.[143,144]

The role of surgery in the management of all forms of vertebral body tuberculosis is controversial[145] and falls beyond the scope of these guidelines. Anecdotal evidence suggests vertebral body tuberculosis associated with paraparesis responds well to medical treatment (which may include corticosteroids) if the MRI shows relatively preserved cord size and oedema with predominantly fluid compression.[146] Patients with extra-dural compression, but with little fluid component compressing or constricting the cord, probably need early surgical decompression.[147] Some centres advocate microsurgical dissection of intra-medullary tuberculomas,[148,149] but it is uncertain which patients should be selected for surgery.

Recommendation
Hydrocephalus, tuberculous cerebral abscess, and vertebral tuberculosis with paraparesis are all indications for neurosurgical referral (A,II). Early ventriculo-peritoneal shunting should be considered in those with non-communicating hydrocephalus (A,II) and in those with communicating hydrocephalus failing medical management (B,II). Communicating hydrocephalus may be treated initially with frusemide (40 mg/24 h adults; 1 mg/kg children) and acetazolamide (10–20 mg/kg adults; 30–50 mg/kg children) (B,II) or repeated lumbar punctures (B,III). Urgent surgical decompression should be considered in all those with extra-dural lesions causing paraparesis (A,II).

Special circumstances

Empirical treatment: when to start, when to stop?

Many patients with CNS tuberculosis require empirical therapy; inevitably, some will receive unnecessary treatment. A recent study, performed in Ecuador, reported that a substantial decrease in the threshold to treat TBM produced only a modest increase in the numbers treated.[150] However, the relationship between treatment threshold and the numbers treated is unlikely to be the same in the UK.

There are no published studies that help determine when empirical therapy should be stopped. Mycobacterial culture results may give additional information, but culture is not sufficiently sensitive to rule out tuberculosis and should not influence treatment decisions if the prior probability of CNS tuberculosis is high. Response to treatment is a poor diagnostic aid: symptoms often worsen after starting treatment for TBM, cerebral tuberculomas take months to resolve,[23,151] and corticosteroids cause symptomatic improvement in many other cerebral diseases.

Recommendation
Delayed anti-tuberculosis treatment of CNS tuberculosis is strongly associated with death and neurological sequelae. The low sensitivity of all currently available rapid diagnostic tests mean empirical therapy may need to be started in many patients with suspected CNS tuberculosis, although it is difficult to stop treatment once started. Therapeutic response (either lack of response or rapid recovery) should not be used to determine when to stop treatment (B,III). We recommend that the safest approach is to give a complete course of treatment in all patients given empirical therapy unless an alternative diagnosis is made (B,III).

How should HIV-infected patients be managed?

Diagnosis

The clinical, laboratory, and radiological features of CNS tuberculosis are similar in HIV infected and uninfected individuals,[152] although concurrent tuberculosis outside the CNS and lung and acellular or neutrophilic CSF is more common in HIV infected patients.[15,153,154] The diagnostic yield of CSF mycobacterial smear and culture is probably higher in patients with HIV infection compared to those uninfected.[153]

A variety of infections and malignancies cause intracerebral mass lesions in patients with HIV, including *Toxoplasma gondii*, progressive multifocal leukoencephalopathy (PML), cryptococcoma, and lymphoma.[155,156] Each may be difficult to distinguish from tuberculosis.[155] South African investigators developed an algorithmic approach to the management of intra-cranial mass lesions in HIV infected patients using CD4+ lymphocyte count, toxoplasmosis serology, routine CSF studies, PCR for *M. tuberculosis* and single positron emission-computed tomography (SPECT).[157] The algorithm correctly identified the aetiology of the lesions in 23/26 patients studied. In settings with low tuberculosis prevalence, response to 2 weeks anti-toxoplasmosis therapy can be used to determine further management in patients with space-occupying lesions without meningitis.[158] Such approaches may obviate the need for brain biopsy in selected cases,[159] but stereotactic brain biopsy, which is associated with low morbidity rates, remains the diagnostic gold standard.[155]

Recommendations
All patients with suspected CNS TB should be tested for HIV (A,II). CSF microscopy, culture, and antigen tests for cryptococcal infection should be performed in addition to mycobacterial tests in all HIV infected patients with suspected CNS infection (A,II). The diagnosis of intra-cerebral mass lesions is difficult. Response to toxoplasmosis empirical therapy may be helpful in those at low demographic risk for tuberculosis and with no evidence of previous or current extra-neural tuberculosis (B,II). In all others, tissue biopsy should be strongly considered (B,III). Other sites of tuberculosis infection should be sought from which tissue specimens might be easily and safely taken (B,III).

Anti-tuberculosis and adjuvant treatment
There is no evidence to suggest HIV infection alters the choice or duration of anti-tuberculosis therapy. The daily administration of rifampicin-containing regimens is widely recommended.[123,124] There are few data to support the use of rifabutin, but it may be necessary to reduce interactions with anti-retroviral therapy. The benefit of adjunctive corticosteroids in HIV infected patients with TBM is uncertain,[125] although data from the only published controlled trial to include HIV infected patients suggested adjunctive dexamethasone might improve outcome.[111]

Combined anti-retroviral and anti-tuberculosis therapy
The management of CNS tuberculosis is complicated in HIV infected patients by the potential for drug interactions, drug toxicity, and paradoxical reactions or immune reconstitution disease (IRD). Detailed information regarding the combined treatment of HIV and tuberculosis is already provided by the British HIV Association (www.bhiva.org) and the Children's HIV Association of UK and Ireland (www.chiva.org.uk). Information concerning the interactions between anti-tuberculosis and anti-retroviral drugs can also be found at www.hiv-druginteractions.org.

It is uncertain whether anti-retroviral therapy should be started with anti-tuberculosis therapy or after a delay. Non-randomised observational studies of all forms of tuberculosis have suggested anti-retroviral treatment probably should not be delayed in those with severe immune suppression (CD4 count <100 cells/μl), but may be delayed for those with higher CD4 counts.[160–162] Definitive evidence from randomised controlled trials is awaited.

IRD — usually manifested by fever and an apparent clinical worsening of disease — has been widely reported in association with CNS tuberculosis.[163] Risk factors include a low CD4 count (usually less than 50 cells/μl), initiation of anti-retroviral therapy shortly after initiation of anti-tuberculosis therapy (typically within 2 months), a rapid fall in viral load and a rise in CD4 cell count.[161,164] In the context of CNS tuberculosis IRD can be life-threatening, with expansion of intracerebral tuberculomas[165,166] or enlargement of spinal lesions reported.[167] The diagnosis of IRD is one of exclusion and non-adherence to therapy, drug resistant *M. tuberculosis*, and other opportunistic infections should be considered.[168] There are currently no diagnostic tools to differentiate between these possibilities.[169] A variety of management strategies have been advocated, including corticosteroids, leukotriene antagonists, and withdrawal of anti-retroviral therapy, but their efficacy remains uncertain.[170]

Recommendations
It is recommended that CNS tuberculosis in HIV infected patients should be managed either within specialist units by physicians with expertise in both HIV and tuberculosis, or in a combined approach between HIV and tuberculosis experts (B,III). Detailed guidance concerning the management of tuberculosis in HIV-infected individuals is provided by the British HIV Association (www.bhiva.org) and the Children's HIV Association of UK and Ireland (www.chiva.org.uk) and the following recommendations should be seen alongside those provided by these organisations.

The anti-tuberculosis drug regimen should be the same as that recommended for HIV uninfected individuals; whenever possible the regimen should include rifampicin (Fig. 4) (B,II). Adjunctive corticosteroids are recommended for those with TBM and HIV infection (B,I).

When to start anti-retroviral therapy depends upon balancing the risks of drug interactions and IRD when started early and opportunistic diseases if the start is delayed (see Table 7 for recommendation in adults). When possible, we recommend treating with rifampicin and a non-nucleoside reverse transcriptase inhibitor (NNRTI), preferably efavirenz (B,III). The dose of efavirenz (standard 600 mg/day) is usually increased to 800 mg/day in patients >60 kg; plasma therapeutic drug concentration measurement can be used to determine if further dose adjustment is necessary (B,II). Rifabutin should be used if treatment with a protease inhibitor (PI) is required, but at a reduced dose (usually 150 mg 3 times per week) (B,II). We do not recommend the co-administration of rifampicin and nevirapine due to the uncertain nature of the interaction, although clinical data in developing world settings has shown good clinical efficacy (B,II). If co-administering efavirenz and rifabutin, increase the daily dose of rifabutin to 450 mg (B,II).

If drug interactions between tuberculosis and HIV therapies do not permit the use of rifampicin, then rifabutin may be substituted with appropriate dose adjustment (B,II) (see www.hiv-druginteractions.org and www.bhiva.org for more detailed information and recommendations).

How should drug resistant disease be treated?

Few studies have examined the relationship between drug resistance and outcome from CNS tuberculosis.[171] Isoniazid resistance has been associated with significantly longer times to CSF sterility in adults with TBM,[48] but a detrimental impact on outcome was not observed when pyrazinamide was used throughout treatment.[107] High or low level isoniazid resistance was not determined in this study, but there is evidence that conventional isoniazid doses are effective in the face of low level resistance.[172,173]

CNS tuberculosis caused by bacteria resistant to at least isoniazid and rifampicin [multi-drug resistance (MDR)] requires alternative therapy.[174,107,175] The World Health Organisation recommend an injectable agent (e.g. amikacin, or capreomycin), ethionamide, pyrazinamide, and a fluoroquinolone (e.g. levofloxacin) for the initial phase of treatment of multi-drug resistant pulmonary tuberculosis.[176] There are no equivalent recommendations for CNS tuberculosis, and few data are available on the CSF penetration and effectiveness of possible agents.[177] Ethionamide, prothionamide, and cycloserine are reported to penetrate the CSF well and may be effective.[116,177] The combination of intra-thecal amikacin and levofloxacin has also been suggested.[178] The fluoroquinolones probably achieve good CSF concentrations early in treatment.[117,119]

Recommendation

The risk of drug resistance must be assessed individually for all patients with CNS tuberculosis (see Fig. 4). The presence of risk factors should prompt rapid susceptibility testing (by molecular and conventional methods) on diagnostic specimens and additional drugs must be strongly considered (B,III). Suspected isoniazid resistant disease (without rifampicin resistance) should be treated initially with conventional 4-drug first-line therapy. If low level resistance is proven, or the cultures are uninformative, we recommend 12 months treatment with rifampicin, isoniazid, and pyrazinamide, with ethambutol stopped after 2 months (B,III). If high level isoniazid resistance is proven we recommend exchanging isoniazid for levofloxacin or moxifloxacin and treat for at least 12 months in combination with rifampicin and pyrazinamide; ethambutol can be stopped after 2 months (B,III).

Patients with suspected or proven MDR CNS tuberculosis should be managed jointly with an MDR TB expert (email mdrtbservice@lhch.nhs.uk). We recommend initial therapy with at least a fluoroquinolone (either moxifloxacin or levofloxacin), pyrazinamide, ethionamide or prothionamide, and an injectable agent (amikacin or capreomycin), unless the susceptibility profile of the index case has shown resistance to any of these agents. Thereafter, treatment should be guided by national MDR experts, individual resistance profiles and the predicted CSF penetration of candidate drugs.

What are the common complications of treatment and how should they be managed?

Hydrocephalus, cerebral infarction, and the expansion of tuberculoma are the commonest reasons for neurological deterioration during the treatment of TBM[12,23] Severe hyponatraemia (<120 mmol/l) may cause deepening coma and seizures. The syndrome of inappropriate anti-diuretic hormone may cause some cases,[179] but reduced plasma volumes and persistent natriuresis despite normal concentrations of anti-diuretic hormone suggest other mechanisms.[180,181] The best way of correcting the sodium is uncertain. There is anecdotal evidence that fludrocortisone replacement therapy and demeclocycline may be useful treatments.[182,183]

Table 7 Recommendation for when to start anti-retroviral drugs in relation to anti-tuberculosis treatment for CNS tuberculosis in adults (B,II).

Peripheral blood total CD4 lymphocyte count	Recommended action
>200 Cells/μl	Defer HIV treatment as long as possible, ideally until end of tuberculosis treatment. Start anti-retroviral treatment if the CD4 count falls below 200 cells/μl during tuberculosis treatment.
100—200 Cells/μl	Start HIV treatment after approximately 2 months of anti-tuberculosis treatment.
<100 Cells/μl	Start HIV treatment within the first 2 weeks of anti-tuberculosis treatment

Clinical deterioration secondary to the expansion of intra-cerebral tuberculoma following the start of anti-tuberculosis drugs — sometimes called paradoxical reactions — are a well-described complication of all forms of cerebral tuberculosis.[126,184] They may also be seen in HIV infected patients in the context of IRD.[163] Intra-cerebral tuberculomas develop during treatment in nearly all patients with TBM,[23] but the majority are clinically silent. A few cause persistent symptoms that, dependent upon their size, location, and number, can be difficult to manage. Corticosteroids may reduce peri-lesional oedema and control symptoms,[126] but can be ineffectual. In these circumstances, small case series support the use of thalidomide[130]; case reports suggest interferon-gamma[185] and infliximab (TNF antibody) may be helpful.[186]

Hepatic toxicity is the commonest serious drug-related event and is associated with old age, malnutrition, alcoholism, HIV infection, and chronic hepatitis B and C infections.[187,188] Drugs may need to be stopped or reduced to prevent hepatic failure, but it is uncertain when this should be done. Liver enzyme abnormalities may resolve spontaneously,[189] but some authorities recommend stopping isoniazid, rifampicin, and pyrazinamide immediately if the serum transaminases rise above five times normal, or if the bilirubin rises.[123,190] Others recommend stopping isoniazid alone if the transaminases rise above three times normal and stopping all drugs if serum albumin falls or the prothrombin time increases.[191] There is a striking lack of evidence for most of these statements. In most forms of tuberculosis a short period without treatment does not affect outcome, but treatment interruptions are an independent risk factor for death from TBM.[111]

A randomised controlled trial of gradual versus immediate reintroduction of the standard drug regimen following drug-induced hepatitis in pulmonary tuberculosis reported significantly fewer hepatitis recurrences when the drugs were reintroduced gradually.[192] Importantly, pyrazinamide was omitted from the gradual reintroduction group, but not the immediate reintroduction group, suggesting this drug may be responsible for recurring hepatitis.

Recommendation

New or worsening neurological signs in patients on treatment for CNS tuberculosis should prompt immediate imaging and neurosurgical review (A,III). Hyponatraemia should be considered as a cause of coma and seizures. Correct the sodium slowly, either by sodium and water replacement if the patient is hypovolaemic, or by fluid restriction if they are euvoleamic (B,III). Fluid restriction is generally not advised in young children, when the risks of dehydration may exceed the benefits of normalising the serum sodium.

When drug-induced hepatitis occurs, the threshold for stopping rifampicin and isoniazid should be higher in those with CNS tuberculosis compared with pulmonary tuberculosis (B,III). If serum transaminases rise above five times normal we recommend stopping pyrazinamide, continuing isoniazid, rifampicin, ethambutol, and performing daily liver function tests (B,II). If serum albumin falls, the prothrombin time rises, or the transaminases continue to rise, isoniazid and rifampicin should be withdrawn (B,II). Streptomycin and ethambutol should be given, and the addition of moxifloxacin or levofloxacin should be considered in those with severe disease (C,III) (N.B. Moxifloxacin can cause hepatitis).

Rifampicin and isoniazid should be restarted immediately the liver function tests are normal. We recommend gradually increasing the dose of both drugs over 5—7 days, with regular (3x/week) liver function tests (see Table 8)(B,III). Pyrazinamide should only be re-started once full-dose rifampicin and isoniazid has been safely re-introduced and it must be given at a gradually increasing dose under close supervision (3x/week liver function tests). If pyrazinamide is not given or tolerated, ethambutol should

Table 8 Suggested regimen for the reintroduction of anti-tuberculosis drugs following drug-induced hepatitis (B,III).[a]

	Isoniazid		Rifampicin		Pyrazinamide
	Adult	Child	Adult	Child	
Day 1	150 mg	5 mg/kg	Omit	Omit	Omit
Day 2	150 mg	5 mg/kg	Omit	Omit	Omit
Day 3	300 mg	10 mg/kg	Omit	Omit	Omit
Day 4	300 mg	10 mg/kg	150 mg	5 mg/kg	Omit
Day 5	300 mg	10—20 mg/kg (max 500 mg)	300 mg	5 mg/kg	Omit
Day 6	300 mg	10—20 mg/kg (max 500 mg)	450 mg	10 mg/kg	Omit
Day 7	300 mg	10—20 mg/kg (max 500 mg)	450 mg (<50 kg) 600 mg (≥50 kg)	10—20 mg/kg (max 600 mg)	Consider gradual reintroduction if normal liver function after 14 days of full-dose rifampicin and isoniazid. If pyrazinamide not used, treat for 18 months

[a] If isoniazid, rifampicin, and pyrazinamide stopped because of drug-induced hepatitis, treat with ethambutol, streptomycin +/− moxifloxacin or levofloxacin until liver function normalises and isoniazid and rifampicin can be re-introduced. Note: moxifloxacin can cause hepatitis.

be given throughout therapy, which should be extended to 18 months (B,III). Streptomycin can be stopped once the full dose of rifampicin and isoniazid are tolerated.

Conflict of interest

None

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Appendix. Clinical Protocol[36,38]

- Close liaison between the clinician caring for the patient and the laboratory staff performing the tests is essential. Limited laboratory resources mean that only CSF from those at substantial risk of having TBM should be submitted for the protocol below
- Additional notes for the clinician:
  Examine CSF before or shortly after starting anti-tuberculosis drugs
  Submit >6mls of CSF exclusively for the staining and culture of *M. tuberculosis*

Appendix. Laboratory Protocol

- Centrifuge at high relative centrifugal force (3000 g) for 20 minutes
- Remove all but 200 μl of supernatant (biochemical tests can be performed on the supernatant if required) and vigorously re-suspend deposit
- Dry two drops of deposit onto a microscope slide (the second directly on top of the first) covering a diameter of less than 1 cm
- Ziehl-Neelsen stain the dried deposit (auromine staining alone is not recommended). Take great care the sample does not detach from the slide when decolourising
- Examine the slide carefully for at least 10 minutes. Search the areas of highest cellularity first. Extend the examination to at least 20 minutes if TBM strongly suspected.

References

1. Rich AR, McCordock HA. The pathogenesis of tuberculous meningitis. *Bull John Hopkins Hosp* 1933;**52**:5—37.
2. Bidstrup C, Andersen PH, Skinhoj P, Andersen AB. Tuberculous meningitis in a country with a low incidence of tuberculosis: still a serious disease and a diagnostic challenge. *Scand J Infect Dis* 2002;**34**(11):811—4.
3. Bishburg E, Sunderam G, Reichman LB, Kapila R. Central nervous system tuberculosis with the acquired immunodeficiency syndrome and its related complex. *Ann Intern Med* 1986; **105**(2):210—3.
4. Keane J. TNF-blocking agents and tuberculosis: new drugs illuminate an old topic. *Rheumatology (Oxford)* 2005;**44**(6): 714—20.
5. Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, et al. Grading quality of evidence and strength of recommendations. *BMJ* 2004;**328**(7454):1490.
6. Girgis NI, Sultan Y, Farid Z, Mansour MM, Erian MW, Hanna LS, et al. Tuberculosis meningitis, Abbassia Fever Hospital-Naval Medical Research Unit No. 3-Cairo, Egypt, from 1976 to 1996. *Am J Trop Med Hyg* 1998;**58**(1):28—34.
7. Hosoglu S, Geyik MF, Balik I, Aygen B, Erol S, Aygencel TG, et al. Predictors of outcome in patients with tuberculous meningitis. *Int J Tuberc Lung Dis* 2002;**6**(1):64—70.
8. Farinha NJ, Razali KA, Holzel H, Morgan G, Novelli VM. Tuberculosis of the central nervous system in children: a 20-year survey. *J Infect* 2000;**41**(1):61—8.
9. Kent SJ, Crowe SM, Yung A, Lucas CR, Mijch AM. Tuberculous meningitis: a 30-year review. *Clin Infect Dis* 1993;**17**(6): 987—94.
10. Verdon R, Chevret S, Laissy JP, Wolff M. Tuberculous meningitis in adults: review of 48 cases. *Clin Infect Dis* 1996;**22**(6): 982—8.
11. Davis LE, Rastogi KR, Lambert LC, Skipper BJ. Tuberculous meningitis in the southwest United States: a community-based study. *Neurology* 1993;**43**(9):1775—8.
12. Thwaites GE, Tran TH. Tuberculous meningitis: many questions, too few answers. *Lancet Neurol* 2005;**4**(3):160—70.
13. Curless RG, Mitchell CD. Central nervous system tuberculosis in children. *Pediatr Neurol* 1991;**7**(4):270—4.
14. Yaramis A, Gurkan F, Elevli M, Soker M, Haspolat K, Kirbas G, et al. Central nervous system tuberculosis in children: a review of 214 cases. *Pediatrics* 1998;**102**(5):E49.
15. Torok ME, Chau TT, Mai PP, Phong ND, Dung NT, Chuong LV, et al. Clinical and microbiological features of HIV-associated tuberculous meningitis in Vietnamese adults. *PLoS ONE* 2008;**3**(3):e1772.
16. Kumar R, Singh SN, Kohli N. A diagnostic rule for tuberculous meningitis. *Arch Dis Child* 1999;**81**(3):221—4.
17. Thwaites GE, Chau TT, Stepniewska K, Phu NH, Chuong LV, Sinh DX, et al. Diagnosis of adult tuberculous meningitis by use of clinical and laboratory features. *Lancet* 2002; **360**(9342):1287—92.
18. Youssef FG, Afifi SA, Azab AM, Wasfy MM, Abdel-Aziz KM, Parker TM, et al. Differentiation of tuberculous meningitis from acute bacterial meningitis using simple clinical and laboratory parameters. *Diagn Microbiol Infect Dis* 2006;**55**(4): 275—8.
19. Torok ME, Nghia HD, Chau TT, Mai NT, Thwaites GE, Stepniewska K, et al. Validation of a diagnostic algorithm for adult tuberculous meningitis. *Am J Trop Med Hyg* 2007; **77**(3):555—9.
20. Sunbul M, Atilla A, Esen S, Eroglu C, Leblebicioglu H. Thwaites' diagnostic scoring and the prediction of tuberculous meningitis. *Med Princ Pract* 2005;**14**(3):151—4.
21. Checkley AM, Njalale Y, Scarborough M. Sensitivity and specificity of an index for the diagnosis of TB meningitis in patients in an urban teaching hospital in Malawi. *Trop Med Int Health*; 2008.
22. Nicolls DJ, King M, Holland D, Bala J, del Rio C. Intracranial tuberculomas developing while on therapy for pulmonary tuberculosis. *Lancet Infect Dis* 2005;**5**(12):795—801.
23. Thwaites GE, Macmullen-Price J, Tran TH, Pham PM, Nguyen TD, Simmons CP, et al. Serial MRI to determine the effect of dexamethasone on the cerebral pathology of tuberculous meningitis: an observational study. *Lancet Neurol* 2007;**6**(3):230—6.

24. Bayindir C, Mete O, Bilgic B. Retrospective study of 23 pathologically proven cases of central nervous system tuberculomas. *Clin Neurol Neurosurg* 2006;**108**(4):353—7.
25. Rajeswari R, Sivasubramanian S, Balambal R, Parthasarathy R, Ranjani R, Santha T, et al. A controlled clinical trial of short-course chemotherapy for tuberculoma of the brain. *Tuber Lung Dis* 1995;**76**(4):311—7.
26. Kalita J, Ranjan P, Misra UK, Das BK. Hemichorea: a rare presentation of tuberculoma. *J Neurol Sci* 2003;**208**(1—2): 109—11.
27. Deogaonkar M, De R, Sil K, Das S. Pituitary tuberculosis presenting as pituitary apoplexy. *Int J Infect Dis* 2006;**10**(4): 338—9.
28. Husain N, Husain M, Rao P. Pituitary tuberculosis mimicking idiopathic granulomatous hypophysitis. *Pituitary*; 2007.
29. Martinez-Vazquez C, Bordon J, Rodriguez-Gonzalez A, de la Fuente-Aguado J, Sopena B, Gallego-Rivera A, et al. Cerebral tuberculoma — a comparative study in patients with and without HIV infection. *Infection* 1995;**23**(3):149—53.
30. du Plessis J, Andronikou S, Theron S, Wieselthaler N, Hayes M. Unusual forms of spinal tuberculosis. *Childs Nerv Syst* 2008; **24**(4):453—7.
31. Hristea A, Constantinescu RV, Exergian F, Arama V, Besleaga M, Tanasescu R. Paraplegia due to non-osseous spinal tuberculosis: report of three cases and review of the literature. *Int J Infect Dis*; 2008.
32. Dastur HM. Diagnosis and neurosurgical treatment of tuberculous disease of the CNS. *Neurosurg Rev* 1983;**6**(3):111—7.
33. Moghtaderi A, Alavi Naini R. Tuberculous radiculomyelitis: review and presentation of five patients. *Int J Tuberc Lung Dis* 2003;**7**(12):1186—90.
34. Chotmongkol V, Kitkuandee A, Limpawattana P. Tuberculous radiculomyelitis (arachnoiditis) associated with tuberculous meningitis. *Southeast Asian J Trop Med Public Health* 2005; **36**(3):722—4.
35. Katchanov J, Bohner G, Schultze J, Klingebiel R, Endres M. Tuberculous meningitis presenting as mesencephalic infarction and syringomyelia. *J Neurol Sci* 2007;**260**(1—2):286—7.
36. Stewart SM. The bacteriological diagnosis of tuberculous meningitis. *Journal of Clinical Pathology* 1953;**6**:241—2.
37. Kennedy DH, Fallon RJ. Tuberculous meningitis. *JAMA* 1979; **241**(3):264—8.
38. Thwaites GE, Chau TT, Farrar JJ. Improving the bacteriological diagnosis of tuberculous meningitis. *J Clin Microbiol* 2004; **42**(1):378—9.
39. Yasuda T, Tomita T, McLone DG, Donovan M. Measurement of cerebrospinal fluid output through external ventricular drainage in one hundred infants and children: correlation with cerebrospinal fluid production. *Pediatr Neurosurg* 2002;**36**(1): 22—8.
40. Rubin RC, Henderson ES, Ommaya AK, Walker MD, Rall DP. The production of cerebrospinal fluid in man and its modification by acetazolamide. *J Neurosurg* 1966;**25**(4):430—6.
41. Huang TY, Chung HW, Chen MY, Giiang LH, Chin SC, Lee CS, et al. Supratentorial cerebrospinal fluid production rate in healthy adults: quantification with two-dimensional cine phase-contrast MR imaging with high temporal and spatial resolution. *Radiology* 2004;**233**(2):603—8.
42. Venkataswamy MM, Rafi W, Nagarathna S, Ravi V, Chandramuki A. Comparative evaluation of BACTEC 460TB system and Lowenstein-Jensen medium for the isolation of *M. tuberculosis* from cerebrospinal fluid samples of tuberculous meningitis patients. *Indian J Med Microbiol* 2007;**25**(3): 236—40.
43. Baker CA, Cartwright CP, Williams DN, Nelson SM, Peterson PK. Early detection of central nervous system tuberculosis with the gen-probe nucleic Acid amplification assay: utility in an inner city hospital. *Clin Infect Dis* 2002;**35**(3):339—42.
44. Rajshekhar V, Abraham J, Chandy MJ. Avoiding empiric therapy for brain masses in Indian patients using CT-guided stereotaxy. *Br J Neurosurg* 1990;**4**(5):391—6.
45. Sumi MG, Mathai A, Sheela R, Radhakrishnan NS, Radhakrishnan VV, Indhulekshmy R, et al. Diagnostic utility of polymerase chain reaction and immunohistochemical techniques for the laboratory diagnosis of intracranial tuberculoma. *Clin Neuropathol* 2001;**20**(4):176—80.
46. Pai M, Flores LL, Pai N, Hubbard A, Riley LW, Colford JM. Diagnostic accuracy of nucleic acid amplification tests for tuberculous meningitis: a systematic review and meta-analysis. *Lancet Infect Dis* 2003;**3**(10):633—43.
47. Dinnes J, Deeks J, Kunst H, Gibson A, Cummins E, Waugh N, et al. A systematic review of rapid diagnostic tests for the detection of tuberculosis infection. *Health Technol Assess* 2007; **11**(3):1—196.
48. Thwaites GE, Caws M, Chau TT, Dung NT, Campbell JI, Phu NH, et al. Comparison of conventional bacteriology with nucleic acid amplification (amplified mycobacterium direct test) for diagnosis of tuberculous meningitis before and after inception of antituberculosis chemotherapy. *J Clin Microbiol* 2004; **42**(3):996—1002.
49. Bhigjee AI, Padayachee R, Paruk H, Hallwirth-Pillay KD, Marais S, Connoly C. Diagnosis of tuberculous meningitis: clinical and laboratory parameters. *Int J Infect Dis* 2007;**11**(4): 348—54.
50. Donald PR, Victor TC, Jordaan AM, Schoeman JF, van Helden PD. Polymerase chain reaction in the diagnosis of tuberculous meningitis. *Scand J Infect Dis* 1993;**25**(5):613—7.
51. Takahashi T, Nakayama T. Novel technique of quantitative nested real-time PCR assay for *Mycobacterium tuberculosis* DNA. *J Clin Microbiol* 2006;**44**(3):1029—39.
52. Takahashi T, Tamura M, Asami Y, Kitamura E, Saito K, Suzuki T, et al. Novel ''wide range'' quantitative nested real-time PCR assay for *Mycobacterium tuberculosis* DNA — development and methodology. *J Clin Microbiol*; 2008.
53. Joos TJ, Miller WC, Murdoch DM. Tuberculin reactivity in bacille Calmette-Guerin vaccinated populations: a compilation of international data. *Int J Tuberc Lung Dis* 2006;**10**(8):883—91.
54. Kilpatrick ME, Girgis NI, Tribble D, Farid Z. The value of the tuberculin skin test in patients with tuberculous meningitis. *J Egypt Public Health Assoc* 1996;**71**(1—2):1—8.
55. Mahadevan B, Mahadevan S, Serane VT, Narasimhan R. Tuberculin reactivity in tuberculous meningitis. *Indian J Pediatr* 2005;**72**(3):213—5.
56. van den Bos F, Terken M, Ypma L, Kimpen JL, Nel ED, Schaaf HS, et al. Tuberculous meningitis and miliary tuberculosis in young children. *Trop Med Int Health* 2004;**9**(2):309—13.
57. Akhila K, Mahadevan S, Adhisivam B. Qualitative evaluation of tuberculin test responses in childhood tuberculosis. *Indian J Pediatr* 2007;**74**(7):641—4.
58. Donald PR, Schoeman JF, Van Zyl LE, De Villiers JN, Pretorius M, Springer P. Intensive short course chemotherapy in the management of tuberculous meningitis. *Int J Tuberc Lung Dis* 1998;**2**(9):704—11.
59. Mann MD, Macfarlane CM, Verburg CJ, Wiggelinkhuizen J. The bromide partition test and CSF adenosine deaminase activity in the diagnosis of tuberculosis meningitis in children. *S Afr Med J* 1982;**62**(13):431—3.
60. Coovadia YM, Dawood A, Ellis ME, Coovadia HM, Daniel TM. Evaluation of adenosine deaminase activity and antibody to *Mycobacterium tuberculosis* antigen 5 in cerebrospinal fluid and the radioactive bromide partition test for the early diagnosis of tuberculosis meningitis. *Arch Dis Child* 1986;**61**(5): 428—35.
61. Lopez-Cortes LF, Cruz-Ruiz M, Gomez-Mateos J, Jimenez-Hernandez D, Jimenez-Mejias E, Pachon J, et al. Adenosine deaminase activity in the CSF of patients with aseptic

meningitis: utility in the diagnosis of tuberculous meningitis or neurobrucellosis. *Clin Infect Dis* 1995;**20**(3):525—30.
62. Mishra OP, Loiwal V, Ali Z, Nath G, Chandra L, Das BK. Cerebrospinal fluid adenosine deaminase activity and C-reactive protein in tuberculous and partially treated bacterial meningitis. *Indian Pediatr* 1995;**32**(8):886—9.
63. Baro M, Acevedo L, Lagos ME. Usefulness of adenosine deaminase determination in cerebrospinal fluid for the diagnosis of meningeal tuberculosis: 4 years experience at a public hospital. *Rev Med Chil* 1996;**124**(3):319—26.
64. Mishra OP, Loiwal V, Ali Z, Nath G, Chandra L. Cerebrospinal fluid adenosine deaminase activity for the diagnosis of tuberculous meningitis in children. *J Trop Pediatr* 1996;**42**(3): 129—32.
65. Gambhir IS, Mehta M, Singh DS, Khanna HD. Evaluation of CSF-adenosine deaminase activity in tubercular meningitis. *J Assoc Physicians India* 1999;**47**(2):192—4.
66. John MA, Coovadia YM. Shortfalls in the use of adenosine deaminase in tuberculous meningitis. *Trop Doct* 2001;**31**(3):138—9.
67. Schutte CM, Ungerer JP, du Plessis H, van der Meyden CH. Significance of cerebrospinal fluid adenosine deaminase isoenzymes in tuberculous (TB) meningitis. *J Clin Lab Anal* 2001; **15**(5):236—8.
68. Corral I, Quereda C, Navas E, Martin-Davila P, Perez-Elias MJ, Casado JL, et al. Adenosine deaminase activity in cerebrospinal fluid of HIV-infected patients: limited value for diagnosis of tuberculous meningitis. *Eur J Clin Microbiol Infect Dis* 2004;**23**(6):471—6.
69. Kashyap RS, Kainthla RP, Mudaliar AV, Purohit HJ, Taori GM, Daginawala HF. Cerebrospinal fluid adenosine deaminase activity: a complimentary tool in the early diagnosis of tuberculous meningitis. *Cerebrospinal Fluid Res* 2006;**3**:5.
70. Kashyap RS, Ramteke SP, Deshpande PS, Purohit HJ, Taori GM, Daginawala HF. Comparison of an adenosine deaminase assay with ELISA for the diagnosis of tuberculous meningitis infection. *Med Sci Monit* 2007;**13**(9):BR200—4.
71. Gautam N, Aryal M, Bhatta N, Bhattacharya SK, Baral N, Lamsal M. Comparative study of cerebrospinal fluid adenosine deaminase activity in patients with meningitis. *Nepal Med Coll J* 2007;**9**(2):104—6.
72. Ferrara G, Losi M, D'Amico R, Roversi P, Piro R, Meacci M, et al. Use in routine clinical practice of two commercial blood tests for diagnosis of infection with Mycobacterium tuberculosis: a prospective study. *Lancet* 2006;**367**(9519):1328—34.
73. Dosanjh DP, Hinks TS, Innes JA, Deeks JJ, Pasvol G, Hackforth S, et al. Improved diagnostic evaluation of suspected tuberculosis. *Ann Intern Med* 2008;**148**(5):325—36.
74. Jafari C, Ernst M, Kalsdorf B, Greinert U, Diel R, Kirsten D, et al. Rapid diagnosis of smear-negative tuberculosis by bronchoalveolar lavage enzyme-linked immunospot. *Am J Respir Crit Care Med* 2006;**174**(9):1048—54.
75. Kosters K, Nau R, Bossink A, Greiffendorf I, Jentsch M, Ernst M, et al. Rapid Diagnosis of CNS tuberculosis by a t-cell interferon-gamma release assay on cerebrospinal fluid mononuclear cells. *Infection*; 2008.
76. Murakami S, Takeno M, Oka H, Ueda A, Kurokawa T, Kuroiwa Y, et al. Diagnosis of tuberculous meningitis due to ESAT-6-specific IFN-gamma production detected by enzyme-linked immunospot assay in cerebrospinal fluid. *Clin Vaccine Immunol*; 2008.
77. Simmons CP, Thwaites GE, Quyen NT, Chau TT, Mai PP, Dung NT, et al. The clinical benefit of adjunctive dexamethasone in tuberculous meningitis is not associated with measurable attenuation of peripheral or local immune responses. *J Immunol* 2005;**175**(1):579—90.
78. Simmons CP, Thwaites GE, Quyen NT, Torok E, Hoang DM, Chau TT, et al. Pretreatment intracerebral and peripheral blood immune responses in Vietnamese adults with tuberculous meningitis: diagnostic value and relationship to disease severity and outcome. *J Immunol* 2006;**176**(3): 2007—14.
79. Yaramis A, Bukte Y, Katar S, Ozbek MN. Chest computerized tomography scan findings in 74 children with tuberculous meningitis in southeastern Turkey. *Turk J Pediatr* 2007; **49**(4):365—9.
80. Ozates M, Kemaloglu S, Gurkan F, Ozkan U, Hosoglu S, Simsek MM. CT of the brain in tuberculous meningitis. A review of 289 patients. *Acta Radiol* 2000;**41**(1):13—7.
81. Srikanth SG, Taly AB, Nagarajan K, Jayakumar PN, Patil S. Clinicoradiological features of tuberculous meningitis in patients over 50 years of age. *J Neurol Neurosurg Psychiatry* 2007;**78**(5):536—8.
82. Koh SB, Kim BJ, Park MH, Yu SW, Park KW, Lee DH. Clinical and laboratory characteristics of cerebral infarction in tuberculous meningitis: a comparative study. *J Clin Neurosci* 2007; **14**(11):1073—7.
83. Chan KH, Cheung RT, Lee R, Mak W, Ho SL. Cerebral infarcts complicating tuberculous meningitis. *Cerebrovasc Dis* 2005; **19**(6):391—5.
84. Hsieh FY, Chia LG, Shen WC. Locations of cerebral infarctions in tuberculous meningitis. *Neuroradiology* 1992;**34**(3): 197—9.
85. Andronikou S, Smith B, Hatherhill M, Douis H, Wilmshurst J. Definitive neuroradiological diagnostic features of tuberculous meningitis in children. *Pediatr Radiol* 2004;**34**(11): 876—85.
86. Abdelmalek R, Kanoun F, Kilani B, Tiouiri H, Zouiten F, Ghoubantini A, et al. Tuberculous meningitis in adults: MRI contribution to the diagnosis in 29 patients. *Int J Infect Dis* 2006;**10**(5):372—7.
87. Oztoprak I, Gumus C, Oztoprak B, Engin A. Contrast medium-enhanced MRI findings and changes over time in stage I tuberculous meningitis. *Clin Radiol* 2007;**62**(12):1206—15.
88. Foerster BR, Thurnher MM, Malani PN, Petrou M, Carets-Zumelzu F, Sundgren PC. Intracranial infections: clinical and imaging characteristics. *Acta Radiol* 2007;**48**(8):875—93.
89. Sonmez G, Ozturk E, Sildiroglu HO, Mutlu H, Cuce F, Senol MG, et al. MRI findings of intracranial tuberculomas. *Clin Imaging* 2008;**32**(2):88—92.
90. Wasay M, Kheleani BA, Moolani MK, Zaheer J, Pui M, Hasan S, et al. Brain CT and MRI findings in 100 consecutive patients with intracranial tuberculoma. *J Neuroimaging* 2003;**13**(3): 240—7.
91. du Plessis J, Andronikou S, Wieselthaler N, Theron S, George R, Mapukata A. CT features of tuberculous intracranial abscesses in children. *Pediatr Radiol* 2007;**37**(2):167—72.
92. Garg RK, Desai P, Kar M, Kar AM. Multiple ring enhancing brain lesions on computed tomography: an Indian perspective. *J Neurol Sci* 2008;**266**(1—2):92—6.
93. Kingsley PB, Shah TC, Woldenberg R. Identification of diffuse and focal brain lesions by clinical magnetic resonance spectroscopy. *NMR Biomed* 2006;**19**(4):435—62.
94. Pretell EJ, Martinot Jr C, Garcia HH, Alvarado M, Bustos JA, Martinot C. Differential diagnosis between cerebral tuberculosis and neurocysticercosis by magnetic resonance spectroscopy. *J Comput Assist Tomogr* 2005;**29**(1):112—4.
95. Moorthy S, Prabhu NK. Spectrum of MR imaging findings in spinal tuberculosis. *AJR Am J Roentgenol* 2002;**179**(4): 979—83.
96. Narlawar RS, Shah JR, Pimple MK, Patkar DP, Patankar T, Castillo M. Isolated tuberculosis of posterior elements of spine: magnetic resonance imaging findings in 33 patients. *Spine* 2002;**27**(3):275—81.
97. Danchaivijitr N, Temram S, Thepmongkhol K, Chiewvit P. Diagnostic accuracy of MR imaging in tuberculous spondylitis. *J Med Assoc Thai* 2007;**90**(8):1581—9.

98. Jung NY, Jee WH, Ha KY, Park CK, Byun JY. Discrimination of tuberculous spondylitis from pyogenic spondylitis on MRI. *AJR Am J Roentgenol* 2004;**182**(6):1405—10.
99. Chang MC, Wu HT, Lee CH, Liu CL, Chen TH. Tuberculous spondylitis and pyogenic spondylitis: comparative magnetic resonance imaging features. *Spine* 2006;**31**(7):782—8.
100. Cordero M, Sanchez I. Brucellar and tuberculous spondylitis. A comparative study of their clinical features. *J Bone Joint Surg Br* 1991;**73**(1):100—3.
101. Parmar H, Shah J, Patkar D, Varma R. Intramedullary tuberculomas. MR findings in seven patients. *Acta Radiol* 2000;**41**(6): 572—7.
102. Sharma A, Goyal M, Mishra NK, Gupta V, Gaikwad SB. MR imaging of tubercular spinal arachnoiditis. *AJR Am J Roentgenol* 1997;**168**(3):807—12.
103. Wasay M, Arif H, Khealani B, Ahsan H. Neuroimaging of tuberculous myelitis: analysis of ten cases and review of literature. *J Neuroimaging* 2006;**16**(3):197—205.
104. Ellard GA, Humphries MJ, Allen BW. Cerebrospinal fluid drug concentrations and the treatment of tuberculous meningitis. *Am Rev Respir Dis* 1993;**148**(3):650—5.
105. Kaojarern S, Supmonchai K, Phuapradit P, Mokkhavesa C, Krittiyanunt S. Effect of steroids on cerebrospinal fluid penetration of antituberculous drugs in tuberculous meningitis. *Clin Pharmacol Ther* 1991;**49**(1):6—12.
106. Mitchison DA. Role of individual drugs in the chemotherapy of tuberculosis. *Int J Tuberc Lung Dis* 2000;**4**(9):796—806.
107. Thwaites GE, Lan NT, Dung NH, Quy HT, Oanh DT, Thoa NT, et al. Effect of antituberculosis drug resistance on response to treatment and outcome in adults with tuberculous meningitis. *J Infect Dis* 2005;**192**(1):79—88.
108. Ellard GA, Humphries MJ, Gabriel M, Teoh R. Penetration of pyrazinamide into the cerebrospinal fluid in tuberculous meningitis. *Br Med J (Clin Res Ed)* 1987;**294**(6567):284—5.
109. Donald PR, Seifart H. Cerebrospinal fluid pyrazinamide concentrations in children with tuberculous meningitis. *Pediatr Infect Dis J* 1988;**7**(7):469—71.
110. Humphries M. The management of tuberculous meningitis. *Thorax* 1992;**47**(8):577—81.
111. Thwaites GE, Nguyen DB, Nguyen HD, Hoang TQ, Do TT, Nguyen TC, et al. Dexamethasone for the treatment of tuberculous meningitis in adolescents and adults. *N Engl J Med* 2004;**351**(17):1741—51.
112. Bobrowitz ID. Ethambutol in tuberculous meningitis. *Chest* 1972;**61**(7):629—32.
113. Gundert-Remy U, Klett M, Weber E. Concentration of ethambutol in cerebrospinal fluid in man as a function of the nonprotein-bound drug fraction in serum. *Eur J Clin Pharmacol* 1973;**6**(2):133—6.
114. WHO. *Anti-tuberculosis drug resistance in the World. Fourth Global Report*. Geneva: World Health Organization; 2008.
115. Donald PR, Maher D, Maritz JS, Qazi S. Ethambutol dosage for the treatment of children: literature review and recommendations. *Int J Tuberc Lung Dis* 2006;**10**(12):1318—30.
116. Donald PR, Seifart HI. Cerebrospinal fluid concentrations of ethionamide in children with tuberculous meningitis. *J Pediatr* 1989;**115**(3):483—6.
117. Barsic B, Himbele J, Beus I, Schonwald S, Marton E, Lisic M. Entry of ciprofloxacin into cerebrospinal fluid during bacterial, viral and tuberculous meningitis. *Neurol Croat* 1991; **40**(2):111—6.
118. Berning SE, Cherry TA, Iseman MD. Novel treatment of meningitis caused by multidrug-resistant *Mycobacterium tuberculosis* with intrathecal levofloxacin and amikacin: case report. *Clin Infect Dis* 2001;**32**(4):643—6.
119. Alffenaar JW, de Vries PM, Luijckx GJ, van Soolingen D, van der Werf TS, van Altena R. Plasma and CSF pharmacokinetics of moxifloxacin in a patient with tuberculous meningitis. *Antimicrobial Agents Chemother*; 2008.
120. Mehlhorn AJ, Brown DA. Safety concerns with fluoroquinolones. *Ann Pharmacother* 2007;**41**(11):1859—66.
121. Diacon AH, Patientia RF, Venter A, van Helden PD, Smith PJ, McIlleron H, et al. Early bactericidal activity of high-dose rifampin in patients with pulmonary tuberculosis evidenced by positive sputum smears. *Antimicrobial Agents Chemother* 2007;**51**(8):2994—6.
122. van Loenhout-Rooyackers JH, Keyser A, Laheij RJ, Verbeek AL, van der Meer JW. Tuberculous meningitis: is a 6-month treatment regimen sufficient? *Int J Tuberc Lung Dis* 2001;**5**(11):1028—35.
123. Treatment of tuberculosis. *MMWR Recomm Rep* 2003;**52**(RR-11):1—77.
124. The National Collaborating Centre for Chronic Conditions. *Tuberculosis: clinical diagnosis and management of tuberculosis, and measures for its prevention and control*. London: Royal College of Physicians; 2006.
125. Prasad K, Singh MB. Corticosteroids for managing tuberculous meningitis. *Cochrane Database Syst Rev* 2008;(1):CD002244.
126. Afghani B, Leiberman JM. Paradoxical enlargement or development of intracranial tuberculomas during therapy: case report and review. *Clin Infect Dis* 1994;**19**:1092—9.
127. Roca B. Intradural extramedullary tuberculoma of the spinal cord: a review of reported cases. *J Infect* 2005;**50**(5):425—31.
128. Roberts MT, Mendelson M, Meyer P, Carmichael A, Lever AM. The use of thalidomide in the treatment of intracranial tuberculomas in adults: two case reports. *J Infect* 2003;**47**(3):251—5.
129. Schoeman JF, Ravenscroft A, Hartzenberg HB. Possible role of adjunctive thalidomide therapy in the resolution of a massive intracranial tuberculous abscess. *Childs Nerv Syst* 2001;**17**(6): 370—2.
130. Schoeman JF, Fieggen G, Seller N, Mendelson M, Hartzenberg B. Intractable intracranial tuberculous infection responsive to thalidomide: report of four cases. *J Child Neurol* 2006;**21**(4):301—8.
131. Schoeman JF, Springer P, van Rensburg AJ, Swanevelder S, Hanekom WA, Haslett PA, et al. Adjunctive thalidomide therapy for childhood tuberculous meningitis: results of a randomized study. *J Child Neurol* 2004;**19**(4):250—7.
132. Schoeman J, Donald P, van Zyl L, Keet M, Wait J. Tuberculous hydrocephalus: comparison of different treatments with regard to ICP, ventricular size and clinical outcome. *Dev Med Child Neurol* 1991;**33**(5):396—405.
133. Mathew JM, Rajshekhar V, Chandy MJ. Shunt surgery in poor grade patients with tuberculous meningitis and hydrocephalus: effects of response to external ventricular drainage and other variables on long term outcome. *J Neurol Neurosurg Psychiatry* 1998;**65**(1):115—8.
134. Kemaloglu S, Ozkan U, Bukte Y, Ceviz A, Ozates M. Timing of shunt surgery in childhood tuberculous meningitis with hydrocephalus. *Pediatr Neurosurg* 2002;**37**(4):194—8.
135. Yadav YR, Pande S, Raina VK, Singh M. Lumboperitoneal shunts: review of 409 cases. *Neurol India* 2004;**52**(2):188—90.
136. Lamprecht D, Schoeman J, Donald P, Hartzenberg H. Ventriculoperitoneal shunting in childhood tuberculous meningitis. *Br J Neurosurg* 2001;**15**(2):119—25.
137. Agrawal D, Gupta A, Mehta VS. Role of shunt surgery in pediatric tubercular meningitis with hydrocephalus. *Indian Pediatr* 2005;**42**(3):245—50.
138. Figaji AA, Fieggen AG, Peter JC. Endoscopy for tuberculous hydrocephalus. *Childs Nerv Syst* 2007;**23**(1):79—84.
139. Jha D, Khatri P, Choudhary A, Sethi R, Kumar S. Endoscopic third ventriculostomy in prepontine-suprasellar tuberculoma with tuberculous meningitis hydrocephalus: a case report. *Pediatr Neurosurg* 2007;**43**(1):42—6.

140. Jha DK, Mishra V, Choudhary A, Khatri P, Tiwari R, Sural A, et al. Factors affecting the outcome of neuroendoscopy in patients with tuberculous meningitis hydrocephalus: a preliminary study. *Surg Neurol* 2007;**68**(1):35—41. discussion 41—2.
141. Tyson G, Newman P, Strachan WE. Tuberculous brain abscess. *Surg Neurol* 1978;**10**(5):323—5.
142. Vidal JE, Penalva de Oliveira AC, Bonasser Filho F, Schiavon Nogueira R, Dauar RF, Leite AG, et al. Tuberculous brain abscess in AIDS patients: report of three cases and literature review. *Int J Infect Dis* 2005;**9**(4):201—7.
143. Mohanty A, Venkatarama SK, Vasudev MK, Khanna N, Anandh B. Role of stereotactic aspiration in the management of tuberculous brain abscess. *Surg Neurol* 1999;**51**(4):443—6. discussion 446—7.
144. Kumar R, Pandey CK, Bose N, Sahay S. Tuberculous brain abscess: clinical presentation, pathophysiology and treatment (in children). *Childs Nerv Syst* 2002;**18**(3—4):118—23.
145. Jutte PC, Van Loenhout-Rooyackers JH. Routine surgery in addition to chemotherapy for treating spinal tuberculosis. *Cochrane Database Syst Rev* 2006;(1):CD004532.
146. Jain AK, Dhammi IK. Tuberculosis of the spine: a review. *Clin Orthop Relat Res* 2007;**460**:39—49.
147. Turgut M. Spinal tuberculosis (Pott's disease): its clinical presentation, surgical management, and outcome. A survey study on 694 patients. *Neurosurg Rev* 2001;**24**(1):8—13.
148. Muthukumar N, Venkatesh G, Senthilbabu S, Rajbaskar R. Surgery for intramedullary tuberculoma of the spinal cord: report of 2 cases. *Surg Neurol* 2006;**66**(1):69—74. discussion 74.
149. Sharma MC, Arora R, Deol PS, Mahapatra AK, Sinha AK, Sarkar C. Intramedullary tuberculoma of the spinal cord: a series of 10 cases. *Clin Neurol Neurosurg* 2002;**104**(4):279—84.
150. Moreira J, Alarcon F, Bisoffi Z, Rivera J, Salinas R, Menten J, et al. Tuberculous meningitis: does lowering the treatment threshold result in many more treated patients? *Trop Med Int Health* 2008;**13**(1):68—75.
151. Poonnoose SI, Rajshekhar V. Rate of resolution of histologically verified intracranial tuberculomas. *Neurosurgery* 2003;**53**(4):873—8. discussion 878—9.
152. Katrak SM, Shembalkar PK, Bijwe SR, Bhandarkar LD. The clinical, radiological and pathological profile of tuberculous meningitis in patients with and without human immunodeficiency virus infection. *J Neurol Sci* 2000;**181**(1—2):118—26.
153. Thwaites GE, Duc Bang N, Huy Dung N, Thi Quy H, Thi Tuong Oanh D, Thi Cam Thoa N, et al. The influence of HIV infection on clinical presentation, response to treatment, and outcome in adults with Tuberculous meningitis. *J Infect Dis* 2005;**192**(12):2134—41.
154. Schutte CM. Clinical, cerebrospinal fluid and pathological findings and outcomes in HIV-positive and HIV-negative patients with tuberculous meningitis. *Infection* 2001;**29**(4):213—7.
155. Skiest DJ. Focal neurological disease in patients with acquired immunodeficiency syndrome. *Clin Infect Dis* 2002;**34**(1):103—15.
156. Offiah CE, Turnbull IW. The imaging appearances of intracranial CNS infections in adult HIV and AIDS patients. *Clin Radiol* 2006;**61**(5):393—401.
157. Smego Jr RA, Orlovic D, Wadula J. An algorithmic approach to intracranial mass lesions in HIV/AIDS. *Int J STD AIDS* 2006;**17**(4):271—6.
158. Antinori A, Ammassari A, De Luca A, Cingolani A, Murri R, Scoppettuolo G, et al. Diagnosis of AIDS-related focal brain lesions: a decision-making analysis based on clinical and neuroradiologic characteristics combined with polymerase chain reaction assays in CSF. *Neurology* 1997;**48**(3):687—94.
159. Menendez JA, Lilien DL, Nanda A, Polin RS. Use of fluorodeoxyglucose-positron emission tomography for the differentiation of cerebral lesions in patients with acquired immune deficiency syndrome. *Neurosurg Focus* 2000;**8**(2):e2.
160. Dean GL, Edwards SG, Ives NJ, Matthews G, Fox EF, Navaratne L, et al. Treatment of tuberculosis in HIV-infected persons in the era of highly active antiretroviral therapy. *AIDS* 2002;**16**(1):75—83.
161. Lawn SD, Myer L, Bekker LG, Wood R. Tuberculosis-associated immune reconstitution disease: incidence, risk factors and impact in an antiretroviral treatment service in South Africa. *AIDS* 2007;**21**(3):335—41.
162. Schiffer JT, Sterling TR. Timing of antiretroviral therapy initiation in tuberculosis patients with AIDS: a decision analysis. *J Acquir Immune Defic Syndr* 2007;**44**(2):229—34.
163. Lawn SD, Bekker LG, Miller RF. Immune reconstitution disease associated with mycobacterial infections in HIV-infected individuals receiving antiretrovirals. *Lancet Infect Dis* 2005;**5**(6):361—73.
164. Shelburne SA, Visnegarwala F, Darcourt J, Graviss EA, Giordano TP, White Jr AC, et al. Incidence and risk factors for immune reconstitution inflammatory syndrome during highly active antiretroviral therapy. *AIDS* 2005;**19**(4):399—406.
165. Crump JA, Tyrer MJ, Lloyd-Owen SJ, Han LY, Lipman MC, Johnson MA. Military tuberculosis with paradoxical expansion of intracranial tuberculomas complicating human immunodeficiency virus infection in a patient receiving highly active antiretroviral therapy. *Clin Infect Dis* 1998;**26**(4):1008—9.
166. Dautremer J, Pacanowski J, Girard PM, Lalande V, Sivignon F, Meynard JL. A new presentation of immune reconstitution inflammatory syndrome followed by a severe paradoxical reaction in an HIV-1-infected patient with tuberculous meningitis. *AIDS* 2007;**21**(3):381—2.
167. Kwara A, Carter EJ, Rich JD, Flanigan TP. Development of opportunistic infections after diagnosis of active tuberculosis in HIV-infected patients. *AIDS Patient Care STDS* 2004;**18**(6):341—7.
168. McIlleron H, Meintjes G, Burman WJ, Maartens G. Complications of antiretroviral therapy in patients with tuberculosis: drug interactions, toxicity, and immune reconstitution inflammatory syndrome. *J Infect Dis* 2007;**196**(Suppl. 1):S63—75.
169. Meintjes G, Lawn SD, Scano F, Maartens G, French MA, Worodria W, et al. Tuberculosis-associated immune reconstitution inflammatory syndrome: case definitions for use in resource-limited settings. *Lancet Infect Dis* 2008;**8**(8):516—23.
170. Dhasmana DJ, Dheda K, Ravn P, Wilkinson RJ, Meintjes G. Immune reconstitution inflammatory syndrome in HIV-infected patients receiving antiretroviral therapy: pathogenesis, clinical manifestations and management. *Drugs* 2008;**68**(2):191—208.
171. Byrd TF, Davis LE. Multidrug-resistant tuberculous meningitis. *Curr Neurol Neurosci Rep* 2007;**7**(6):470—5.
172. Cynamon MH, Zhang Y, Harpster T, Cheng S, DeStefano MS. High-dose isoniazid therapy for isoniazid-resistant murine Mycobacterium tuberculosis infection. *Antimicrobial Agents Chemother* 1999;**43**(12):2922—4.
173. Abate G, Hoffner SE, Thomsen VO, Miorner H. Characterization of isoniazid-resistant strains of *Mycobacterium tuberculosis* on the basis of phenotypic properties and mutations in katG. *Eur J Clin Microbiol Infect Dis* 2001;**20**(5):329—33.
174. Patel VB, Padayatchi N, Bhigjee AI, Allen J, Bhagwan B, Moodley AA, et al. Multidrug-resistant tuberculous meningitis in KwaZulu-Natal, South Africa. *Clin Infect Dis* 2004;**38**(6):851—6.
175. Daikos GL, Cleary T, Rodriguez A, Fischl MA. Multidrug-resistant tuberculous meningitis in patients with AIDS. *Int J Tuberc Lung Dis* 2003;**7**(4):394—8.
176. Organisation WH. Guidelines for the pragmatic management of drug-resistant tuberculosis, 2006.
177. Holdiness MR. Cerebrospinal fluid pharmacokinetics of the antituberculosis drugs. *Clin Pharmacokinet* 1985;**10**(6):532—4.
178. Berning SE. The role of fluoroquinolones in tuberculosis today. *Drugs* 2001;**61**(1):9—18.
179. Cotton MF, Donald PR, Schoeman JF, Van Zyl LE, Aalbers C, Lombard CJ. Raised intracranial pressure, the syndrome of inappropriate antidiuretic hormone secretion, and arginine

vasopressin in tuberculous meningitis. *Childs Nerv Syst* 1993; **9**(1):10—5. discussion 15—6.
180. Narotam PK, Kemp M, Buck R, Gouws E, van Dellen JR, Bhoola KD. Hyponatremic natriuretic syndrome in tuberculous meningitis: the probable role of atrial natriuretic peptide. *Neurosurgery* 1994;**34**(6):982—8. discussion 988.
181. Dass R, Nagaraj R, Murlidharan J, Singhi S. Hyponatraemia and hypovolemic shock with tuberculous meningitis. *Indian J Pediatr* 2003;**70**(12):995—7.
182. Celik US, Alabaz D, Yildizdas D, Alhan E, Kocabas E, Ulutan S. Cerebral salt wasting in tuberculous meningitis: treatment with fludrocortisone. *Ann Trop Paediatr* 2005;**25**(4):297—302.
183. Smith J, Godwin-Austen R. Hypersecretion of anti-diuretic hormone due to tuberculous meningitis. *Postgrad Med J* 1980;**56**(651):41—4.
184. Chambers ST, Hendrickse WA, Record C, Rudge P, Smith H. Paradoxical expansion of intracranial tuberculomas during chemotherapy. *Lancet* 1984;**2**(8396):181—4.
185. Coulter JB, Baretto RL, Mallucci CL, Romano MI, Abernethy LJ, Isherwood DM, et al. Tuberculous meningitis: protracted course and clinical response to interferon-gamma. *Lancet Infect Dis* 2007;**7**(3):225—32.
186. Blackmore TK, Manning L, Taylor WJ, Wallis RS. Therapeutic use of infliximab in tuberculosis to control severe paradoxical reaction of the brain and lymph nodes. *Clin Infect Dis* 2008; **47**(10):e83—5.
187. Yew WW, Leung CC. Antituberculosis drugs and hepatotoxicity. *Respirology* 2006;**11**(6):699—707.
188. Tostmann A, Boeree MJ, Aarnoutse RE, de Lange WC, van der Ven AJ, Dekhuijzen R. Antituberculosis drug-induced hepatotoxicity: concise up-to-date review. *J Gastroenterol Hepatol* 2008;**23**(2):192—202.
189. Frontera Izquierdo P, Unceta Aguirre L, Tomas Vila M, Calvo Rigual F, Perez Tamarit D. Hepatotoxicity of rifampicin and isoniazid in the treatment of tuberculous meningitis (author's transl). *An Esp Pediatr* 1981;**15**(6):549—52.
190. British Thoracic Society. Chemotherapy and management of tuberculosis in the United Kingdom: recommendations 1998. Joint Tuberculosis Committee of the British Thoracic Society. *Thorax* 1998;**53**(7):536—48.
191. Thompson NP, Caplin ME, Hamilton MI, Gillespie SH, Clarke SW, Burroughs AK, et al. Anti-tuberculosis medication and the liver: dangers and recommendations in management. *Eur Respir J* 1995;**8**(8):1384—8.
192. Tahaoglu K, Atac G, Sevim T, Tarun T, Yazicioglu O, Horzum G, et al. The management of anti-tuberculosis drug-induced hepatotoxicity. *Int J Tuberc Lung Dis* 2001; **5**(1):65—9.
193. Girgis NI, Farid Z, Kilpatrick ME, Sultan Y, Mikhail IA. Dexamethasone adjunctive treatment for tuberculous meningitis. *Pediatr Infect Dis J* 1991;**10**(3):179—83.
194. Schoeman JF, Van Zyl LE, Laubscher JA, Donald PR. Effect of corticosteroids on intracranial pressure, computed tomographic findings, and clinical outcome in young children with tuberculous meningitis. *Pediatrics* 1997; **99**(2):226—31.