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

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Organisations represented: none.

Organisations represented: British HIV Association (BHIVA).

Organisations represented: none.

Organisations represented: Association of British Neurologists.

Organisations represented: British Infection Society and British Thoracic Society.

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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
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. 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; in high tuberculosis prevalence countries CNS tuberculosis predominately affects very young children (<3 years). In low tuberculosis prevalence countries such as the UK, most cases are in adults, often immigrants from areas of high tuberculosis prevalence. Immune-suppressed adults, especially those with HIV infection, are more likely to suffer disseminated disease with CNS involvement. Other risk factors include alcoholism, diabetes mellitus, malignancy, corticosteroid treatment, and agents that block the action of tumour necrosis factor.

**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. 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. 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 (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
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%), 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/mm³ 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.13,34 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 1 Rating system for the strength of the guidelines recommendations and the quality of the evidence.5

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

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

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Frequency/range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>50–80%</td>
</tr>
<tr>
<td>Fever</td>
<td>60–95%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>30–60%</td>
</tr>
<tr>
<td>Photophobia</td>
<td>5–10%</td>
</tr>
<tr>
<td>Anorexia/weight loss</td>
<td>60–80%</td>
</tr>
<tr>
<td>Clinical sign</td>
<td></td>
</tr>
<tr>
<td>Neck stiffness</td>
<td>40–80%</td>
</tr>
<tr>
<td>Confusion</td>
<td>10–30%</td>
</tr>
<tr>
<td>Coma</td>
<td>30–60%</td>
</tr>
<tr>
<td>Cranial nerve palsy</td>
<td>30–50%</td>
</tr>
<tr>
<td>VI</td>
<td>30–40%</td>
</tr>
<tr>
<td>III</td>
<td>5–15%</td>
</tr>
<tr>
<td>VII</td>
<td>10–20%</td>
</tr>
<tr>
<td>Hemiparesis</td>
<td>10–20%</td>
</tr>
<tr>
<td>Paraparesis</td>
<td>5–10%</td>
</tr>
<tr>
<td>Seizures — children</td>
<td>50%</td>
</tr>
<tr>
<td>Adults</td>
<td>5%</td>
</tr>
<tr>
<td>Cerebrospinal fluid</td>
<td></td>
</tr>
<tr>
<td>Clear appearance</td>
<td>80–90%</td>
</tr>
<tr>
<td>Opening pressure &gt;25 cm H₂O</td>
<td>50%</td>
</tr>
<tr>
<td>Leucocyte count (×10³/mL)</td>
<td>5–1000</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>10–70%</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>30–90%</td>
</tr>
<tr>
<td>Protein (g/L)</td>
<td>0.45–3.0⁸</td>
</tr>
<tr>
<td>Lactate (mmol/L)</td>
<td>5.0–10.0</td>
</tr>
<tr>
<td>CSF glucose:blood glucose</td>
<td>&lt; 0.5 95%</td>
</tr>
</tbody>
</table>

⁸ Cerebrospinal protein can be >10 g/l in those with spinal block.
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, but only 15–20% of children. Positive CSF smear and culture is independently associated with large volumes (>6 ml) of CSF submitted for examination; repeated lumbar punctures and CSF examination also increase diagnostic yield. M. tuberculosis has been isolated from significantly smaller CSF volumes from HIV infected than uninfected individuals. 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 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 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 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. Immuno-histochemical detection of M. tuberculosis antigens in tissue has been reported by Indian researchers to be more sensitive than bacteriology or PCR.

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%). Most studies conclude that commercial NAA tests

| 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) | More than 6 days of symptoms Optic atrophy Abnormal movements Focal neurological deficit Neutrophils forming less than half the total numbers of CSF leucocytes | ≥1 variable present (98% sensitive, 44% specific) |
| Children and adults rule (5 months to 56 years) | Duration of symptoms greater than 5 days Clear CSF CSF white cell count < 1000 × 10³/ml Lymphocytes >30% of total number of CSF white cells CSF protein >100 mg/dl | ≥2 variables present (97% sensitive, 57% specific) |
| Adult rule (>15 years) | Age ≥ 36 years (score +2) or < 36 (score 0) Blood WCC (10⁹/ml) ≥15000 (score +4) or <15000 (score 0) History of illness ≥ 6 days (score −5) or < 6 days (score 0) CSF total WCC (10³/ml) ≥750 (score +3) or < 750 (score 0) CSF neutrophils ≥ 90% (score +4) or < 90% (score 0) | Total score ≤ + 4 = TBM Total score > + 4 = bacterial meningitis (90–99% sensitive, 79–82% specific) |
Figure 1: Diagnosis of TB meningitis 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).

** 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.
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.

Interferon-gamma release assays (IGRA)
Recent studies suggest 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. Whether these assays can be adapted to diagnose active tuberculosis is uncertain. The detection of interferon-gamma-producing T-cells in bronchial-alveolar lavage fluid has been used successfully to diagnose pulmonary tuberculosis and case reports suggest similar assays may be useful in the diagnosis of TBM. However, others have found that CSF lymphocytes die rapidly when stimulated with M. tuberculosis specific antigens ex vivo and the test fails. 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.

Recommendation
CSF adenosine deaminase activity is not recommended as a routine diagnostic test for CNS tuberculosis (B,II). The tuberculin skin test and IGRA (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, IGRA 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; 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.

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

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).

** CSF volumes should be adjusted according to the age of the patient - see Table 4.
Figure 3  Diagnosis of spinal cord TB in adults and children.
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.\textsuperscript{85}

Magnetic resonance imaging (MRI) provides high definition of infra-tentorial lesions and the early cerebral changes of TBM,\textsuperscript{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.\textsuperscript{88}

Figure 4 Management of TB meningitis in children and adults.
Cerebral tuberculoma without meningoitis
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 CH2 peak has been used to specifically identify tuberculomas93; others have suggested tuberculomas can be distinguished from neurocysticercosis on the basis of choline/creatinine 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.96,97 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 freely104,105 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 outcomes of CNS tuberculosis, although it is well absorbed orally and achieves high concentrations in the CSF.108,109 Isoniazid, rifampicin and pyrazinamide are considered mandatory at the beginning of TBM treatment110 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 meninges116 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 TBM101 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, and there are no data to suggest higher doses improve outcome or shorten treatment in adults. Rifampicin penetrates the CNS less well than isoniazid and high doses (20 mg/kg to a maximum of 600 mg) are reported to be well tolerated in children and may increase the early bacterial kill. 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. Once through the intensive phase of treatment, doses can be reduced to standard levels. 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.

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. However, most authorities recommend 12 months treatment, 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?

**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. Anecdotally, they improve symptom and seizure control and reduce tuberculoma size and peri-lesional oedema. 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. 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.

**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>
<thead>
<tr>
<th>Drug</th>
<th>Daily dose</th>
<th>Route</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>10–20 mg/kg (max 500 mg)</td>
<td>Oral</td>
<td>12 Months</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>10–20 mg/kg (max 600 mg)</td>
<td>Oral</td>
<td>12 Months</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>30–35 mg/kg (max 2 g)</td>
<td>Oral</td>
<td>2 Months</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>15–20 mg/kg (max 1 g)</td>
<td>Oral</td>
<td>2 Months</td>
</tr>
</tbody>
</table>
Table 6  Corticosteroid regimens used in controlled trials associated with significant improvements in outcome.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Girgis et al.</th>
<th>Schoeman et al.</th>
<th>Thwaites et al.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of subjects</td>
<td>60% &lt;14 years (median 8 years)</td>
<td>&lt;14 years</td>
<td>&gt;14 years</td>
</tr>
<tr>
<td>MRC Grade</td>
<td>All grades</td>
<td>Grade II and III</td>
<td>Grade I</td>
</tr>
<tr>
<td>Drug</td>
<td>Dexamethasone</td>
<td>Prednisolone</td>
<td>Dexamethasone</td>
</tr>
<tr>
<td>Time</td>
<td>Dose/route</td>
<td>Dose/route</td>
<td>Dose/route</td>
</tr>
<tr>
<td>Week 1</td>
<td>12 mg/day im (8 mg/day if &lt;25 kg)</td>
<td>4 mg/kg/day</td>
<td>0.3 mg/kg/day</td>
</tr>
<tr>
<td>Week 2</td>
<td>12 mg/day im (8 mg/day if &lt;25 kg)</td>
<td>4 mg/kg/day</td>
<td>0.2 mg/kg/day</td>
</tr>
<tr>
<td>Week 3</td>
<td>12 mg/day im (8 mg/day if &lt;25 kg)</td>
<td>4 mg/kg/day</td>
<td>0.1 mg/kg/day</td>
</tr>
<tr>
<td>Week 4</td>
<td>Reducing over 3 weeks to stop</td>
<td>3 mg total/day</td>
<td>Reducing by 1 mg each</td>
</tr>
<tr>
<td>Week 5</td>
<td>Reducing dose to stop</td>
<td>oral</td>
<td>week over 2 weeks</td>
</tr>
</tbody>
</table>

Reduction 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. 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, although outcomes are variable. Response to external ventricular drainage has failed to predict those who benefit from early shunting. Endoscopic third ventriculostomy is advocated by some centres as an alternative to shunt surgery.

Rarely, tuberculomas coalesce and liquefy to cause tuberculomas, but it is uncertain which patients should be selected for surgery. 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. 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, 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, although concurrent tuberculosis outside the CNS and lung and acellular or neutrophilic CSF is more common in HIV infected patients. The diagnostic yield of CSF mycobacterial smear and culture is probably higher in patients using CD4 lymphocyte counts, toxoplasmosis serology, routine CSF studies, PCR for M. tuberculosis and single positron emission-computed tomography (SPECT). 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. Such approaches may obviate the need for brain biopsy in selected cases, but stereotactic brain biopsy, which is associated with low morbidity rates, remains the diagnostic gold standard.

Recommendations
All patients with suspected CNS TB should be tested for HIV (A,II). CSF microscopy, culture, and antigen tests for mycobacterial infection should be performed in addition to mycobacterial tests in all HIV infected patients with suspected CNS infection (A,II). The diagnosis 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). 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. Such approaches may obviate the need for brain biopsy in selected cases, but stereotactic brain biopsy, which is associated with low morbidity rates, remains the diagnostic gold standard.

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. 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, although data from the only published controlled trial to include HIV infected patients suggested adjunctive dexamethasone might improve outcome.

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.

IRD — usually manifested by fever and an apparent clinical worsening of disease — has been widely reported in association with CNS tuberculosis. 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. In the context of CNS tuberculosis IRD can be life-threatening, with expansion of intra-cerebral tuberculumas or enlargement of spinal lesions reported. The diagnosis of IRD is one of exclusion and non-adherence to therapy, drug resistant M. tuberculosis, and other opportunistic infections should be considered. There are currently no diagnostic tools to differentiate between these possibilities. A variety of management strategies have been advocated, including corticosteroids, leukotriene antagonists, and withdrawal of anti-retroviral therapy, but their efficacy remains uncertain.

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. Isoniazid resistance has been associated with significantly longer times to CSF sterility in adults with TBM, but a detrimental impact on outcome was not observed when pyrazinamide was used throughout treatment. 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.

CNS tuberculosis caused by bacteria resistant to at least isoniazid and rifampicin [multi-drug resistance (MDR)] requires alternative therapy. 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. There are no equivalent recommendations for CNS tuberculosis, and few data are available on the CSF penetration and effectiveness of possible agents. Ethionamide, prothionamide, and cycloserine are reported to penetrate the CSF well and may be effective. The combination of intra-thecal amikacin and levofloxacin has also been suggested. The fluoroquinolones probably achieve good CSF concentrations early in treatment.

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 mdrbservice@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. Severe hypotraëmia (<120 mmol/l) may cause deepening coma and seizures. The syndrome of inappropriate anti-diuretic hormone may cause some cases, but reduced plasma volumes and persistent natriuresis despite normal concentrations of anti-diuretic hormone suggest other mechanisms. The best way of correcting the sodium is uncertain. There is anecdotal evidence that fludrocortisone replacement therapy and demeclocycline may be useful treatments.

<table>
<thead>
<tr>
<th>Table 7</th>
<th>Recommendation for when to start anti-retroviral drugs in relation to anti-tuberculosis treatment for CNS tuberculosis in adults (B,II).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral blood total CD4 lymphocyte count</td>
<td>Recommended action</td>
</tr>
<tr>
<td>&gt;200 Cells/μl</td>
<td>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.</td>
</tr>
<tr>
<td>100–200 Cells/μl</td>
<td>Start HIV treatment after approximately 2 months of anti-tuberculosis treatment.</td>
</tr>
<tr>
<td>&lt;100 Cells/μl</td>
<td>Start HIV treatment within the first 2 weeks of anti-tuberculosis treatment.</td>
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</table>
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. They may also be seen in HIV infected patients in the context of IRD. Intra-cerebral tuberculomas develop during treatment in nearly all patients with TBM, 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, but can be ineffectual. In these circumstances, small case series support the use of thalidomide; case reports suggest interferon-gamma and infliximab (TNF antibody) may be helpful.

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. 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, but some authorities recommend stopping isoniazid, rifampicin, and pyrazinamide immediately if the serum transaminases rise above five times normal, or if the bilirubin rises. 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.

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. 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. 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 euvoalemic. 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. If serum transaminases rise above five times normal we recommend stopping pyrazinamide, continuing isoniazid, rifampicin, ethambutol, and performing daily liver function tests. If serum albumin falls, the prothrombin time rises, or the transaminases continue to rise, isoniazid and rifampicin should be withdrawn. Streptomycin and ethambutol should be given, and the addition of moxifloxacin or levofloxacin should be considered in those with severe disease. 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).

| 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 | 5 mg/kg |
| Day 5 | 300 mg | 10–20 mg/kg (max 500 mg) | 300 mg | 5 mg/kg | 5 mg/kg |
| 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) |

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

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*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

- 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.

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