

Recent advances in the diagnosis and management of tuberculous meningitis

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Abstract

Purpose: Tuberculous meningitis is a devastating infection that is hard to diagnose and treat. We have reviewed tuberculous meningitis original research published within the last 18 months, selecting papers which we consider have most advanced knowledge.

Recent findings: We review advances in diagnostic methods, anti-tuberculosis chemotherapy, and the common complications of tuberculous meningitis. New commercial molecular diagnostic tests, such as GeneXpert MTB/RIF, have an important role in tuberculous meningitis diagnosis, but as with all other available tests they lack sensitivity and cannot rule out the disease. Recent trials and pharmacokinetic studies have advanced understanding of the best anti-tuberculosis drug regimens for tuberculous meningitis, although optimal doses and duration remain uncertain, especially for young children. Good outcomes depend upon the careful management of the common complications (brain infarcts, tuberculomas, hydrocephalus and hyponatraemia) and controlling intracranial pressure. New tools, such as point-of-care ultrasound, may assist in the management, especially in the assessment of intravascular volume and raised intracranial pressure.

Summary: Disability-free survival from tuberculous meningitis depends upon rapid diagnosis, starting anti-tuberculosis drugs before the onset of coma, and managing complications. Progress is slow and threatened by emerging drug resistant bacteria, but new drugs and diagnostic technologies offer hope to future patients.

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Introduction

Mycobacterium tuberculosis can cause disease, or tuberculosis, in almost any organ. However, when it infects the brain and causes tuberculous meningitis (TBM) the consequences are severe, resulting in death or disability in almost half of all sufferers despite anti-tuberculosis chemotherapy [1].

TBM typically presents as a sub-acute or chronic meningitis, with many days or weeks of headache, fever and vomiting, culminating in loss of consciousness, focal neurological deficit and death, unless anti-tuberculosis chemotherapy is given. The primary challenge for physicians worldwide is making the diagnosis and starting treatment sufficiently quickly to reduce the risk of death or long-term neurological disability. However, once the decision to treat is made, many questions remain concerning the best anti-tuberculosis drug regimen, whether all patients should receive adjunctive anti-inflammatory treatment, and how the common complications of the disease should be managed.

The difficulties of diagnosing and treating TBM have been the subject of much research over the last 50 years, although the relative rarity of the disease compared with pulmonary tuberculosis, the difficulties confirming the diagnosis, and its severity, have hampered progress. Here, we review the published literature on TBM since January 1st 2015, highlighting the most significant publications and advances made over the last 20 months to August 18th, 2016. During this period a PubMed search on 'tuberculosis' gave 12,458 publications; narrowing the search to 'tuberculous meningitis' gave 214 publications, or 2% of the total tuberculosis publications and highlighting the continued paucity of information on this lethal infection.

The diagnosis of TBM

The cornerstones of TBM diagnosis for much of the world remain the 130-year old Ziehl-Neelsen (ZN) stain to visualize *M. tuberculosis* by microscopy in the cerebrospinal fluid (CSF), and bacterial culture. Microscopy is notoriously insensitive (~10%), unless large CSF volumes are examined by highly skilled, meticulous microscopists [2], and culture is too slow for clinical decision-making and is often unavailable outside large centres. Nucleic acid amplification techniques, such as those based on polymerase chain reaction (PCR), have long promised to overcome the inadequacies of conventional microbiology, but to-date have been disappointing. They too have lacked sensitivity – generally being no more than 50% sensitive compared to clinical diagnosis – and requires laboratory facilities and expertise that are rarely available in resource-poor settings.

The GeneXpert MTB/RIF (Cepheid, USA) is a commercial, cartridge based nucleic acid amplification test which detects DNA sequences specific for *M. tuberculosis* and rifampicin resistance in clinical specimens in around 2 hours. It has been endorsed by the WHO for use in resource-limited, tuberculosis endemic countries since 2010. The first studies investigating GeneXpert for TBM diagnosis [3,4] indicated that the test was highly specific (94-99%), but only around 60% sensitive, although sensitivity increased (up to ~80%) in HIV-infected individuals. These studies, and one recently published [5], have confirmed that prior CSF centrifugation substantially enhances sensitivity from around 30% to 70%.

However, GeneXpert lacks the sensitivity and negative predictive value to confidently rule out TBM [6,7]. Alternatives have been investigated; including loop-mediated isothermal amplification (LAMP), which amplifies DNA in a single tube at a constant temperature (thereby avoiding the thermal cycle of PCR), making it potentially more suitable for resource-limited settings. Modi et al recently compared LAMP with conventional PCR for TBM diagnosis in 250 Indian patients with meningitis (150 had TBM) and demonstrated that the LAMP assay was more sensitive than PCR (75% versus 85%) and retained high specificity [8]. Whether LAMP can out-perform its PCR-based commercial rivals remains to be investigated.

The limitations of nucleic acid amplification have led to investigations detecting *M. tuberculosis* specific lipoarabinomannan (LAM) in CSF. Investigators in Uganda compared the detection of LAM by lateral flow assay (LFA) or enzyme-linked immunosorbent assay (ELISA) with GeneXpert in CSF from an autopsy cohort of 91 HIV-infected adults [9]. In those with histopathological TBM confirmation, the sensitivity of LAM LFA was 75%, ELISA 43%, and Xpert MTB/RIF 100%, suggesting LAM LFA could be a useful test. However, as others have suggested [10], the clinical applicability of these results needs confirmation: post-mortem 4th ventricle CSF may have dissimilar properties to lumbar CSF taken in life, and others have found LAM LFA to be substantially less sensitive in the clinical setting [11].

The difficulty of detecting *M. tuberculosis* in the CSF has driven interest in whether specific immune responses can aid TBM diagnosis. Interferon gamma release assays (IGRAs) depend upon the ability of T-lymphocytes to produce interferon- γ when stimulated with *M. tuberculosis*-specific antigens; those previously infected with *M. tuberculosis* produce higher concentrations than uninfected individuals. Over the last decade a number of studies have investigated IGRAs for TBM diagnosis and their combined findings were reported in a recent systematic review and metaanalysis [12]. Eight studies using blood IGRA and 6 studies using CSF IGRA for TBM diagnosis were included. The overall sensitivity of blood and CSF IGRA were 78% and 77% respectively; with 61% and 88% specificity. These current data suggest these assays are only moderately useful; their specificity is enhanced when used on CSF, but large volumes are required (>2mls) and indeterminate results are common (up to 15%). In our opinion, these tests hold no current advantage over GeneXpert.

In summary, TBM diagnosis remains a major clinical challenge. Without a high sensitivity assay which can 'rule out' TBM, and given the fatal consequences of delayed diagnosis, the majority of patients will be treated 'empirically' on the basis of compatible clinical features. When possible, CSF ZN stain, mycobacterial culture, and GeneXpert should all be performed, but their limitations must be recognised.

Anti-tuberculosis therapy

Anti-tuberculosis chemotherapy is undergoing a quiet revolution. For the first time in decades new drugs are appearing and the use of old drugs, such as rifampicin, is being re-evaluated. Even the relatively neglected world of TBM therapeutics has been enlivened by these advances with a small explosion of data over the last year [13].

Ever since streptomycin turned tuberculosis into a treatable disease in the 1940s, it has been uncertain whether TBM should be treated with the same drugs, doses and durations as pulmonary tuberculosis.

There has been long-standing recognition that some of the key anti-tuberculosis drugs, rifampicin in particular, do not penetrate the blood-brain barrier well. Arising from these observations, and driven by TBM's stubbornly high morbidity and mortality, is the attractive hypothesis that 'intensifying' the anti-tuberculosis TBM treatment will improve outcomes.

Support for the hypothesis was strengthened in 2013 with the publication of a small but carefully conducted randomized controlled trial in Indonesia that reported mortality in adults with TBM fell from 65% to 35% when rifampicin (combined with other anti-tuberculosis drugs) was given intravenously at higher dose (~13mg/kg) compared to orally at standard dose (~10mg/kg) for the first 14 days of treatment [14]. Subsequent pharmacokinetic analysis showed surviving patients had significantly higher rifampicin exposure (Area-under-the-curve (AUC) concentrations in plasma and CSF, and higher CSF maximum concentrations) than those who died [15].

The same investigators went on to investigate whether higher oral rifampicin doses of ~17 and ~20mg/kg for the first 14 days of TBM treatment lead to rifampicin exposures equivalent to intravenous rifampicin at ~13mg/kg [16]. Rifampicin pharmacokinetics was assessed ≤ 3 days after treatment initiation and ≥ 9 days in 30 adults with TBM randomly allocated to each rifampicin dose. In the first days of treatment, the geometric mean (range) plasma AUC₀₋₂₄ values following rifampicin ~17mg/kg orally, ~20mg/kg mg orally and ~13mg/kg mg intravenously were 131.4 (38.1-275.1), 164.8 (66.9-291.2) and 145.7 (77.7-430.2) mg·h/L, respectively. After ≥ 9 days, AUC₀₋₂₄ values had decreased to 100.1, 101.2 and 94.9 mg·h/L, reflecting rifampicin's ability to induce its own metabolism. Higher doses were not associated with increased risk of drug-induced liver injury. The study was too small to link increased rifampicin exposure to outcome, but suggest relatively modest increases in oral rifampicin dose lead to drug exposure equivalent to the 13mg/kg intravenous dose which was associated with such a dramatic increase in TBM survival.

Against mounting evidence that 'intensifying' anti-tuberculosis treatment may improve TBM outcomes, came the results of the largest randomised controlled trial ever conducted in TBM [17]. 817 Vietnamese adults with TBM were randomly allocated treatment with either a standard oral anti-tuberculosis regimen consisting of isoniazid (5mg/kg/day), rifampicin (10mg/kg/day), pyrazinamide (25mg/kg/day) and ethambutol (20mg/kg/day) for 3 months, followed by rifampicin and isoniazid at the same doses for a further 6 months, or the same regimen with higher dose oral rifampicin (15mg/kg/day) and levofloxacin (20 mg/kg/day) for the first 8 weeks of treatment. The results, published in January 2016, were disappointing [17]. The intensified treatment regimen was not associated with improved survival or any other measure of treatment response. Only those with TBM caused by isoniazid resistant bacteria showed any suggestion of benefit from the intensified regimen.

The failure of the intensified regimen to improve outcomes in this trial provoked much discussion [18-20]. Pharmacokinetic sub-studies from the trial are awaited, but the rifampicin CSF exposures may not have been as high as those achieved in the Indonesian study when the drug was given intravenously. If this is the case, the desire to explore intensified anti-tuberculosis treatment is unlikely to end and even higher doses of rifampicin, possibly administered intravenously for the first few weeks, will require further investigation in large pragmatic clinical trials. In the meantime, we suggest current treatment

guidelines should not change for drug-susceptible TBM. However, if isoniazid resistant disease is strongly suspected or confirmed then higher rifampicin doses and the addition of a fluoroquinolone (e.g. levofloxacin) may improve outcomes. In rifampicin and isoniazid resistance (multi-drug resistance) is suspected then ≥ 4 second-line anti-tuberculosis drugs must be started as early as possible.

Uncertainty concerning the optimal doses and duration of anti-tuberculosis drugs is especially acute in the treatment of childhood TBM. The WHO currently recommend children with TBM should be treated for 12 months with the same dosing used for pulmonary tuberculosis treatment, which includes rifampicin at 15mg/kg (range 10-20mg/kg) [21]. Many clinicians, however, opt for higher doses. South African paediatricians have long used a 6-month hyperintensive regimen, consisting of 20mg/kg of isoniazid, rifampicin and ethionamide and pyrazinamide 40 mg/kg, with excellent results [22]. Furthermore, a recent pharmacokinetic modeling study strongly suggested that children require daily rifampicin doses of at least 30 mg/kg orally or 15 mg/kg intravenously to achieve target exposure [23]. Controlled trials examining higher dose, shorter regimens are urgently required in children; so too are studies examining the utility of newer drugs. A recent retrospective study suggested linezolid may improve outcomes in childhood TBM [24], but this needs confirmation in prospective controlled studies. The new anti-tuberculosis drugs delamanid and bedaquiline may hold promise, especially when the bacteria are resistant to first-line drugs. There are no published data on the CSF pharmacokinetics or clinical efficacy of delamanid, but one recent case-report suggested very poor CSF bedaquiline penetration in an adult with TBM [25].

Clinical complications and pathogenesis

Disability-free survival from TBM is not solely dependent on the activity of anti-tuberculosis drugs. Brain infarction, hydrocephalus, tuberculoma formation and severe hyponatraemia are common, life-threatening complications that can occur before or during anti-tuberculosis treatment. Each requires active management, although the strategies that lead to the best outcomes are largely unknown. Adjunctive corticosteroids undoubtedly play a role, but whilst they increase survival they probably do not reduce disability [26].

Infarcts are a common cause of TBM-related neuro-disability. To investigate the frequency and pathogenesis of TBM-related infarcts, 101 HIV-uninfected adults with TBM from Guangzhou, China underwent magnetic resonance angiography (MRA) at diagnosis with prospective clinical follow-up [27]. Imaging revealed hydrocephalus in 21%, tuberculomas in 33% and infarcts in 37%. 51% of the infarcts involved the head of the caudate nucleus, anteromedial thalami and anterior limb and genu of the internal capsule (the so-called 'tubercular zone'). MRA was abnormal in 45% (45/91) of patients, predominantly with multi-focal abnormalities of the anterior circulatory system. Focal stenosis of large arteries (the middle cerebral artery most commonly) was correlated with disease severity and clinical stroke. These findings were complimented by a post-mortem study performed in India of 51 patients of all ages who died from TBM [28]. Vascular involvement was almost universal and infarcts were found in 37 cases, more commonly in the middle cerebral artery territory. Microscopic infarctions in the brainstem and cerebellum were much more common than reported by radiological studies. These two important studies demonstrate the high frequency of disseminated vascular involvement, even in mild

disease, although around one third were sub-clinical. More research is required to combat the vascular complications of TBM.

Paradoxical reactions, or the development of new symptoms associated with new or worsening pre-existing tuberculous lesions after the start of anti-tuberculosis chemotherapy, are well-described for all forms of tuberculosis. They present special difficulties when they involve the brain, but their nature, incidence and impact upon long-term outcome is not well-described. Singh et al prospectively studied 141 consecutively treated Indian adults with TBM and reported 31% developed a paradoxical reaction, almost all within 3 months of starting anti-tuberculosis treatment [29]. The commonest reactions were tuberculoma formation (26 patients), new hydrocephalus (20 patients), and optochiasmatic (7 patients) or spinal arachnoiditis (4 patients). These reactions were associated with an increase in CSF cells, predominantly neutrophils, and protein, but did not appear to worsen longer-term outcomes. The mechanisms behind these inflammatory reactions are unclear, but there are parallels with tuberculosis-associated immune reconstitution inflammatory syndrome (IRIS) in HIV-infected adults. A recent South African study reported high baseline *M. tuberculosis* antigen load was strongly associated with TBM neurological IRIS, as were an increase in CSF neutrophils and their mediators [30].

One the hardest complications of TBM to manage is hyponatraemia (plasma sodium <135mmol/L), which occurs in 30-50% of patients in the first month of treatment. The difficulties stem from its uncertain pathogenesis and scant data concerning best management. Misra et al prospectively studied 76 Indian patients of all ages with TBM to determine the frequency, cause and prognosis of hyponatraemia [31]. Thirty-four patients (45%) of patients had hyponatraemia, which was moderate or severe (<130mmol/L) in 31. Hyponatraemia was due to cerebral salt wasting in 17, syndrome of inappropriate anti-diuretic hormone in 3, and various other causes in 14 (e.g. diuretics, vomiting, Addison's disease). Cerebral salt wasting was more common in those with more severe disease, suggesting fluid/sodium replacement may be the right treatment approach in these patients.

In practice, brain ischemia, hydrocephalus and raised intracranial pressure (ICP), hyponatremia, and seizures are all common and often overlapping problems in those with severe TBM and should not be viewed in isolation. To date, however, the holistic care of critically ill patients with TBM has received little attention [32]. The use of portable 'point-of-care' ultrasound is now being widely used to guide clinical decision-making at bedside of critically ill patients [33]. Point-of-care ultrasound could be of particular benefit to the management of TBM through the accurate assessment of intravascular volume (when trying to determine the likely cause and best treatment of hyponatraemia) and by providing non-invasive estimates of ICP [34,35]. The ability to monitor ICP through treatment and track the consequences and management of the common TBM complications would be a major advance. The first paper describing sonographic measurement of optic nerve sheath diameter to assess ICP in TBM was published in 2015 [36]. This preliminary study demonstrated the technique was safe and relatively simple and showed TBM was associated with increased sheath diameters compared with controls. They did not, however, link their observations to disease severity, complications of treatment outcomes.

Conclusions

TBM is difficult to diagnose and treat. GeneXpert represents the most significant advance in TBM diagnostics over the last decade, but it lacks sensitivity and cannot be used to rule out the diagnosis. A rapid, accurate and affordable diagnostic test is much needed but publications over the last 18 months do not suggest its arrival is imminent. In comparison, greater advances have been made concerning the anti-tuberculosis chemotherapy of TBM with the publication of clinical trials and pharmacokinetic studies exploring the use of higher rifampicin doses and fluoroquinolones. Although none of the data will change current treatment guidelines, understanding the relationships between CSF drug exposure and treatment outcomes has improved substantially over the last 18 months bringing greater clarity to the requirement and design of future clinical trials. Still neglected, however, is the care of those critically ill with severe TBM, and the pathogenesis and optimal treatment of the common complications. Lastly, the rise of drug-resistant TBM threatens to reverse many of the recent advances. TBM caused by multi-drug (at least isoniazid and rifampicin) resistant organisms results in death or severe disability in almost all sufferers. Unless better methods to detect and treat drug-resistant TBM are developed, the future for many patients with TBM is bleak.

Bullet points:

- GeneXpert MTB/RIF test on CSF can be used to rule in the diagnosis of TBM, but not to rule it out
- The blood-brain barrier may limit the effectiveness of some anti-tuberculosis drugs in the treatment of TBM and may necessitate higher doses or different drugs, but recent large clinical trials suggest 'hyperintensive' regimens only benefit those with drug-resistant infections
- The management of those critically ill with severe TBM - often suffering from raised intracranial pressure, hydrocephalus, brain infarction and hyponatraemia - is important but frequently neglected and should receive more attention.

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Conflicts of interest

We have no conflicts of interest.

References

References of special interest are marked * and given a brief annotation. References which are of outstanding interest should be marked ** and given a longer annotation.

1. Thwaites GE, van Toorn R, Schoeman J: **Tuberculous meningitis: more questions, still too few answers.** *Lancet Neurol* 2013, **12**:999-1010.
2. Thwaites GE, Chau TT, Farrar JJ: **Improving the bacteriological diagnosis of tuberculous meningitis.** *J Clin Microbiol* 2004, **42**:378-379.
3. Patel VB, Theron G, Lenders L, Matinyena B, Connolly C, Singh R, Coovadia Y, Ndung'u T, Dheda K: **Diagnostic accuracy of quantitative PCR (Xpert MTB/RIF) for tuberculous meningitis in a high burden setting: a prospective study.** *PLoS Med* 2013, **10**:e1001536.
4. Nhu NT, Heemskerk D, Thu do DA, Chau TT, Mai NT, Nghia HD, Loc PP, Ha DT, Merson L, Thinh TT, et al.: **Evaluation of GeneXpert MTB/RIF for diagnosis of tuberculous meningitis.** *J Clin Microbiol* 2014, **52**:226-233.
5. Bahr NC, Tugume L, Rajasingham R, Kiggundu R, Williams DA, Morawski B, Alland D, Meya DB, Rhein J, Boulware DR: **Improved diagnostic sensitivity for tuberculous meningitis with Xpert((R)) MTB/RIF of centrifuged CSF.** *Int J Tuberc Lung Dis* 2015, **19**:1209-1215.
6. Boyles TH, Thwaites GE: **Appropriate use of the Xpert(R) MTB/RIF assay in suspected tuberculous meningitis.** *Int J Tuberc Lung Dis* 2015, **19**:276-277.
7. Bahr NC, Marais S, Caws M, van Crevel R, Wilkinson RJ, Tyagi JS, Thwaites GE, Boulware DR, Tuberculous Meningitis International Research C: **GeneXpert MTB/Rif to Diagnose Tuberculous Meningitis: Perhaps the First Test but not the Last.** *Clin Infect Dis* 2016, **62**:1133-1135.
8. Modi M, Sharma K, Sharma M, Sharma A, Sharma N, Sharma S, Ray P, Varma S: **Multitargeted loop-mediated isothermal amplification for rapid diagnosis of tuberculous meningitis.** *Int J Tuberc Lung Dis* 2016, **20**:625-630.
9. Cox JA, Lukande RL, Kalungi S, Van Marck E, Lammens M, Van de Vijver K, Kambugu A, Nelson AM, Colebunders R, Manabe YC: **Accuracy of Lipoarabinomannan and Xpert MTB/RIF Testing in Cerebrospinal Fluid To Diagnose Tuberculous Meningitis in an Autopsy Cohort of HIV-Infected Adults.** *J Clin Microbiol* 2015, **53**:2667-2673.
10. Bahr NC, Tugume L, Boulware DR: **A Word of Caution in Considering the Use of the Lipoarabinomannan Lateral Flow Assay on Cerebrospinal Fluid for Detection of Tuberculous Meningitis.** *J Clin Microbiol* 2016, **54**:241-242.
11. Patel VB, Bhigjee AI, Paruk HF, Singh R, Meldau R, Connolly C, Ndung'u T, Dheda K: **Utility of a novel lipoarabinomannan assay for the diagnosis of tuberculous meningitis in a resource-poor high-HIV prevalence setting.** *Cerebrospinal Fluid Res* 2009, **6**:13.
12. Yu J, Wang ZJ, Chen LH, Li HH: **Diagnostic accuracy of interferon-gamma release assays for tuberculous meningitis: a meta-analysis.** *Int J Tuberc Lung Dis* 2016, **20**:494-499.
13. Nguyen TH, Thwaites GE: **The current pharmacological landscape of tuberculous meningitis: where to next?** *Expert Rev Clin Pharmacol* 2016, **9**:625-627.
14. Ruslami R, Ganiem AR, Dian S, Apriani L, Achmad TH, van der Ven AJ, Borm G, Aarnoutse RE, van Crevel R: **Intensified regimen containing rifampicin and moxifloxacin for tuberculous meningitis: an open-label, randomised controlled phase 2 trial.** *Lancet Infect Dis* 2013, **13**:27-35.
15. Te Brake L, Dian S, Ganiem AR, Ruesen C, Burger D, Donders R, Ruslami R, van Crevel R, Aarnoutse R: **Pharmacokinetic/pharmacodynamic analysis of an intensified regimen containing rifampicin and moxifloxacin for tuberculous meningitis.** *Int J Antimicrob Agents* 2015, **45**:496-503.*

Provides important data underpinning the finding that higher dose intravenous rifampicin may improve survival from TBM, supporting the notion that higher rifampicin exposures are directly responsible for the effect.

16. Yunivita V, Dian S, Ganiem AR, Hayati E, Hanggono Achmad T, Purnama Dewi A, Teulen M, Meijerhof-Jager P, van Crevel R, Aarnoutse R, et al.: **Pharmacokinetics and safety/tolerability of higher oral and intravenous doses of rifampicin in adult tuberculous meningitis patients.** *Int J Antimicrob Agents* 2016.*

Intravenous rifampicin isn't widely available and this study provides key information concerning the oral doses likely to give equivalent exposures to the intravenous dose which was associated with improved survival from TBM.

17. Heemskerk AD, Bang ND, Mai NT, Chau TT, Phu NH, Loc PP, Chau NV, Hien TT, Dung NH, Lan NT, et al.: **Intensified Antituberculosis Therapy in Adults with Tuberculous Meningitis.** *N Engl J Med* 2016, **374**:124-134.**

The largest randomised controlled trial ever conducted in TBM, which demonstrated moderate increases in rifampicin dose and the addition of levofloxacin to the first 2 months of standard 4-drug treatment did not increase survival, except in those with disease caused by isoniazid resistant bacteria. Linked pharmacokinetic studies eagerly awaited to be able to compare rifampicin exposures with the Indonesian intravenous rifampicin study.

18. van Crevel R, Ruslami R, Aarnoutse R: **Therapy for Tuberculous Meningitis.** *N Engl J Med* 2016, **374**:2187.
19. Boeree MJ, Gillespie SH, Hoelscher M, Pan Act: **Therapy for Tuberculous Meningitis.** *N Engl J Med* 2016, **374**:2187-2188.
20. Heemskerk AD, Bang ND, Thwaites GE: **Therapy for Tuberculous Meningitis.** *N Engl J Med* 2016, **374**:2188-2189.
21. Organization WH: **Guidance for national tuberculosis programmes on the management of tuberculosis in children.** edn Second. Edited by. Geneva; 2014.
22. van Toorn R, Schaaf HS, Laubscher JA, van Elsland SL, Donald PR, Schoeman JF: **Short intensified treatment in children with drug-susceptible tuberculous meningitis.** *Pediatr Infect Dis J* 2014, **33**:248-252.
23. Savic RM, Ruslami R, Hibma JE, Hesselning A, Ramachandran G, Ganiem AR, Swaminathan S, McIlleron H, Gupta A, Thakur K, et al.: **Pediatric tuberculous meningitis: Model-based approach to determining optimal doses of the anti-tuberculosis drugs rifampin and levofloxacin for children.** *Clin Pharmacol Ther* 2015, **98**:622-629.*

The anti-tuberculosis treatment of young children with TBM is controversial, with gathering evidence that much higher doses of rifampicin, in particular, is required than those currently recommended by international guidelines. This modelling study suggests rifampicin at 30mg/kg/day - twice the current WHO recommended dose - is needed to achieve adequate CSF exposures.

24. Li H, Lu J, Liu J, Zhao Y, Ni X, Zhao S: **Linezolid is Associated with Improved Early Outcomes of Childhood Tuberculous Meningitis.** *Pediatr Infect Dis J* 2016, **35**:607-610.

25. Akkerman OW, Odish OF, Bolhuis MS, de Lange WC, Kremer HP, Luijckx GJ, van der Werf TS, Alffenaar JW: **Pharmacokinetics of Bedaquiline in Cerebrospinal Fluid and Serum in Multidrug-Resistant Tuberculous Meningitis.** *Clin Infect Dis* 2016, **62**:523-524.
26. Prasad K, Singh MB, Ryan H: **Corticosteroids for managing tuberculous meningitis.** *Cochrane Database Syst Rev* 2016, **4**:CD002244.
27. Lu TT, Lin XQ, Zhang L, Cai W, Dai YQ, Lu ZZ, Wu AM, Bao J, Yang Y, Hu XQ, et al.: **Magnetic resonance angiography manifestations and prognostic significance in HIV-negative tuberculosis meningitis.** *Int J Tuberc Lung Dis* 2015, **19**:1448-1454.
28. Chatterjee D, Radotra BD, Vasishta RK, Sharma K: **Vascular complications of tuberculous meningitis: An autopsy study.** *Neurol India* 2015, **63**:926-932.*

Autopsy studies underpin much of our understanding of TBM pathogenesis, but most were conducted more than 50 years ago. But as this study demonstrates, they are a valuable source of information and provide important insights into the pathology responsible for death and disability.

29. Singh AK, Malhotra HS, Garg RK, Jain A, Kumar N, Kohli N, Verma R, Sharma PK: **Paradoxical reaction in tuberculous meningitis: presentation, predictors and impact on prognosis.** *BMC Infect Dis* 2016, **16**:306.
30. Marais S, Wilkinson KA, Lesosky M, Coussens AK, Deffur A, Pepper DJ, Schutz C, Ismail Z, Meintjes G, Wilkinson RJ: **Neutrophil-associated central nervous system inflammation in tuberculous meningitis immune reconstitution inflammatory syndrome.** *Clin Infect Dis* 2014, **59**:1638-1647.
31. Misra UK, Kalita J, Bhoi SK, Singh RK: **A study of hyponatremia in tuberculous meningitis.** *J Neurol Sci* 2016, **367**:152-157.**

This study provides the first systematic study of hyponatraemia in TBM, a key complication of TBM and one which is extremely difficult to manage. The finding that cerebral salt wasting is probably responsible for the most severe cases has direct implications for patient management.

32. Figaji AA, Fieggen AG: **The neurosurgical and acute care management of tuberculous meningitis: evidence and current practice.** *Tuberculosis (Edinb)* 2010, **90**:393-400.
33. Whitson MR, Mayo PH: **Ultrasonography in the emergency department.** *Crit Care* 2016, **20**:227.
34. Kelly N, Esteve R, Papadimos TJ, Sharpe RP, Keeney SA, DeQuevedo R, Portner M, Bahner DP, Stawicki SP: **Clinician-performed ultrasound in hemodynamic and cardiac assessment: a synopsis of current indications and limitations.** *Eur J Trauma Emerg Surg* 2015, **41**:469-480.
35. Ohle R, McIsaac SM, Woo MY, Perry JJ: **Sonography of the Optic Nerve Sheath Diameter for Detection of Raised Intracranial Pressure Compared to Computed Tomography: A Systematic Review and Meta-analysis.** *J Ultrasound Med* 2015, **34**:1285-1294.
36. Sangani SV, Parikh S: **Can sonographic measurement of optic nerve sheath diameter be used to detect raised intracranial pressure in patients with tuberculous meningitis? A prospective observational study.** *Indian J Radiol Imaging* 2015, **25**:173-176.