Tuberculous Meningitis in Children: a Review of the Literature

with special thanks to Dr. Jeff Starke

Silvia S. Chiang, M.D.
Clinical Postdoctoral Fellow
Pediatric Infectious Diseases

I have no conflicts of interest to disclose.

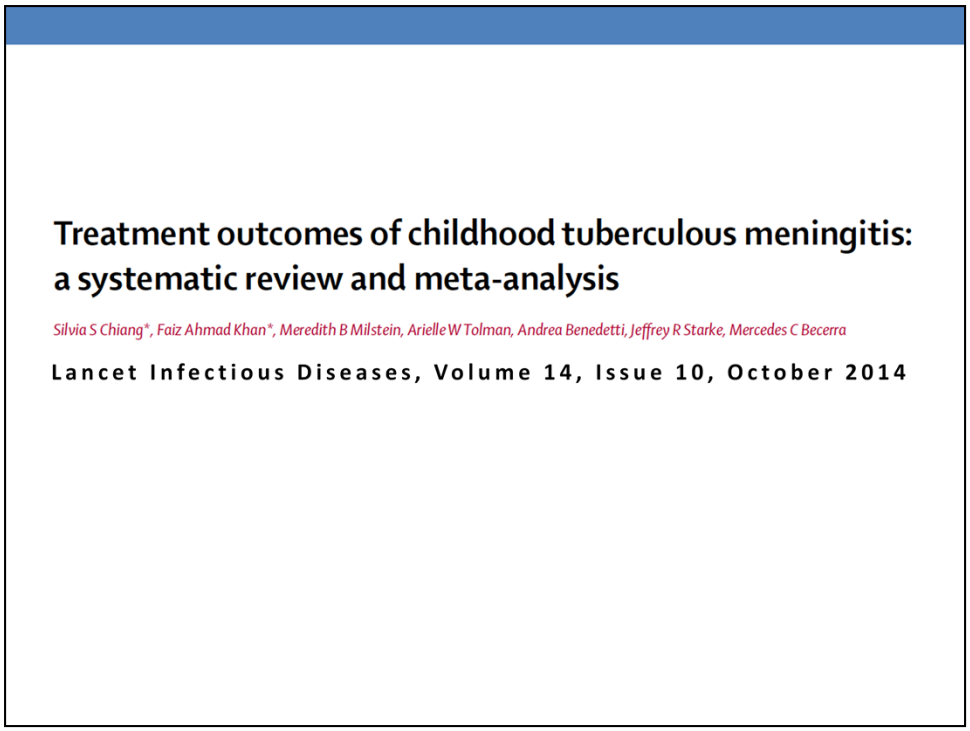
I have no disclosures

Objectives

1. Be familiar with the existing scope of the childhood TB meningitis literature and remaining research gaps

2. Appreciate the diagnostic challenges and poor outcomes of childhood TB meningitis and the need for prompt, empirical TB treatment in a child with suspected TB meningitis

3. Recognize the most common signs, symptoms, and diagnostic findings in childhood TBM



Much of the evidence I will present in my talk is drawn from a recent systematic review and meta-analysis that I led. We assessed treatment outcome for >1600 children diagnosed with TB meningitis in 10 different countries in a 50-year period. We also looked at patient and treatment factors that could affect outcomes, and we also pooled the frequencies of symptoms and diagnostic findings on presentation.

(To perform the meta-analysis, we used random effects models w/ the exact binomial method)

Significance of TB Meningitis

- Deadliest, most debilitating form of TB
- Estimated to occur in 0.7-1.0% of childhood TB cases[1]
- Higher risk in infants and toddlers

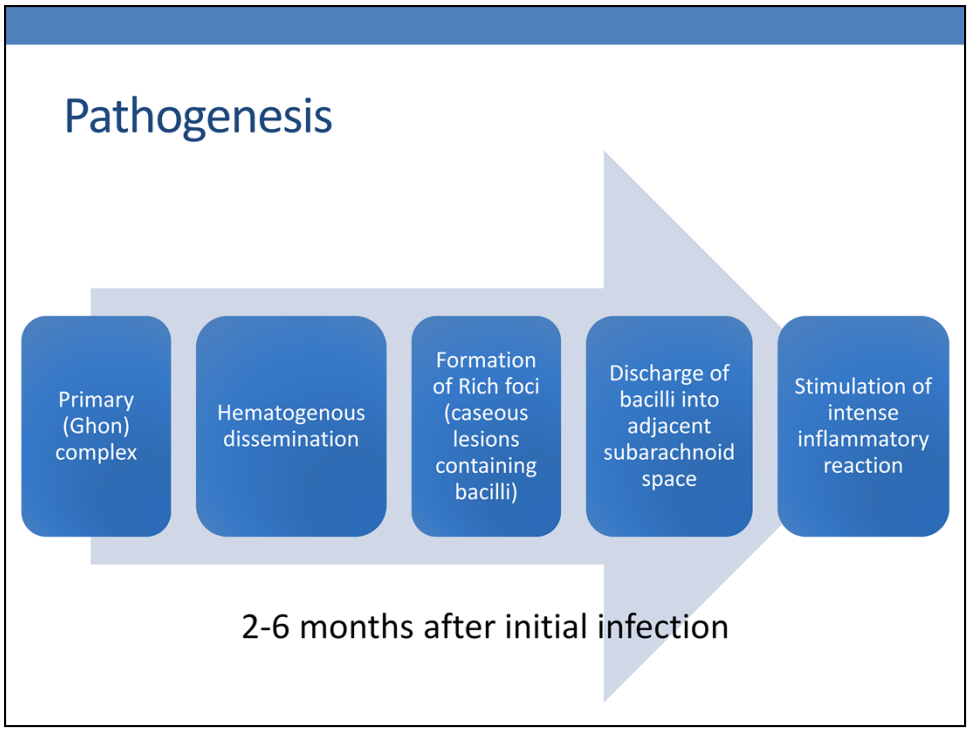
[1]Trunz BB et al. Lancet 2006;367: 1173-80.

Before availability of anti-TB antibiotics, killed within 3-4 weeks

Even w/ antibiotics, prognosis is not great, as I will show with some of our data

So if there are 1 million cases of childhood TB a year, then there would be about 10,000 cases of childhood TBM a year

In areas with high rates of TB and vaccination against pneumococcus, Hib, and meningococcus, TB is becoming more epidemiologically important. In 2012, an area in South Africa reported that tuberculosis was a more common cause of childhood meningitis than those other 3 pathogens combined.



The airway is the typical portal of entry for TB. When the TB germs settle in the lungs, they stimulate an inflammatory reaction and together with the macrophages, form an inflammatory focus. The TB germs also spread through nearby lymphatic vessels to regional lymph nodes. This triad of the inflammatory focus, lymphangitis, and the regional lymphadenopathy is known as the primary complex. In most healthy individuals, the infection is contained within the primary complex. However, if the immune system cannot contain the infection within the primary complex, TB can spread through the bloodstream and the lymphatic system to distant sites, including the brain. And this is why immunocompromised patients, including young children, whose immune systems are weak and immature, are most vulnerable to TB meningitis.

In the brain, the TB germs are situated in areas of caseation called Rich foci. These foci eventually discharge TB into the adjacent subarachnoid space, thus causing meningitis. Of note, typically in TB meningitis, the inflammatory reaction is most severe at the base of the brain.

Direct massive seeding of the meninges may occur but is rare

Inflammation is most intense at the base of the brain

Accumulation of cells, hyperemia, edema, capillary damage, exudate and

fibrosis ensue

Serous TB meningitis: Rich focus causes lymphocytic reaction of adjacent subarachnoid space w/o actual seeding of TB—was only nonfatal form of TB meningitis in pre-ABX era

Usually occurs 2-6 months after infection

Accompanied by miliary TB in ~50% of cases

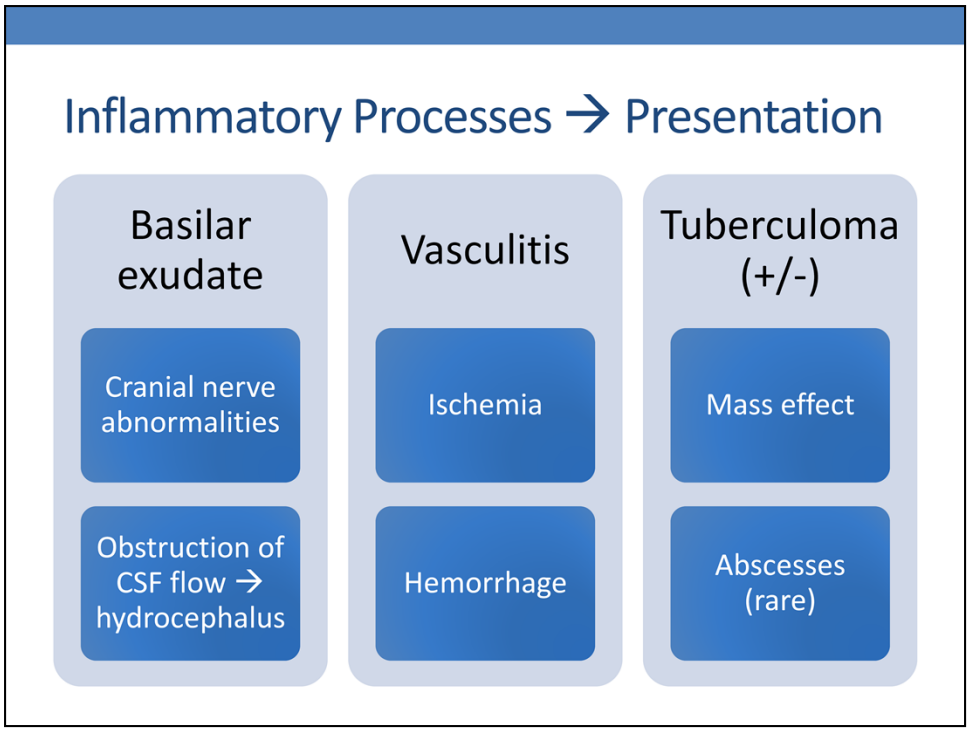
Hypersensitivity phase: T cell-mediated response, manifested by fever, TST conversion, formation of Ghon complex on CXR

LN ~2-12 months

Pleural effusion 3-9 months

Skeletal 6-24 months

Renal 1-5 years



The primary inflammatory processes involved in TB meningitis are basilar exudate, vasculitis, and sometimes tuberculoma. TB causes the most intense inflammation at the base of the brain. Basilar exudate leads to CN abnormalities and obstruction of CSF flow, which can result in . . .

These three processes are

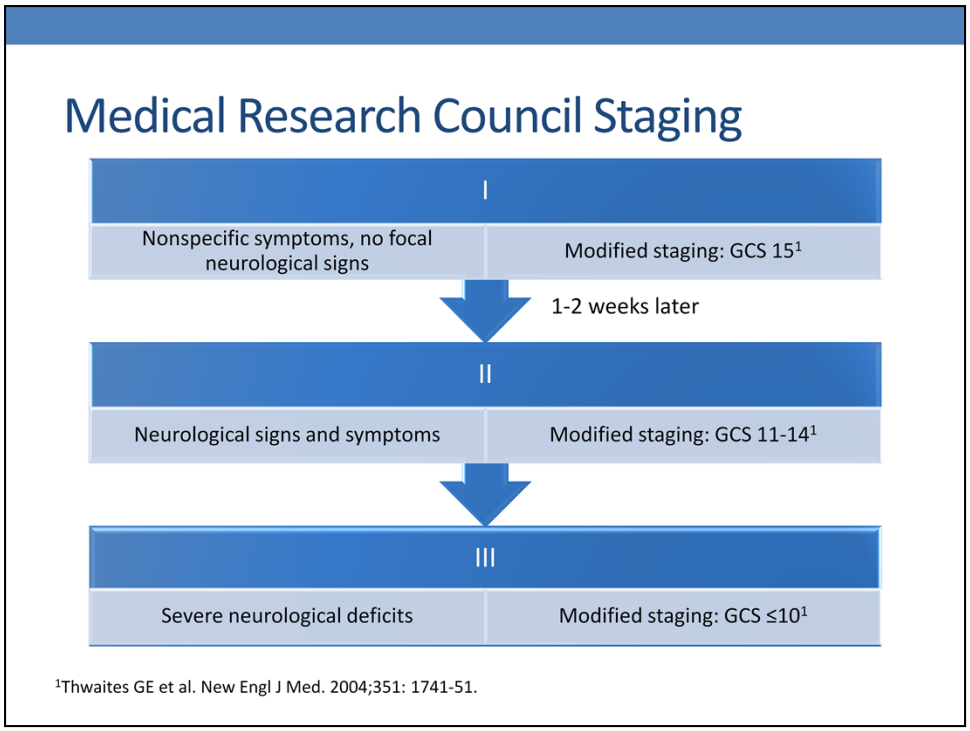
TUBERCULOMA

- Small areas of necrosis form in the cortex
- Lesions enlarge and aggregate, forming a macroscopic nodule that does not rupture into the subarachnoid space
- Local hypersensitivity reaction causes edema and PMN infiltration
- Often infratentorial
- If the necrosis in the brain is extensive, a tuberculous brain abscess may form

IRIS

- Occurs in patients with dual TB and HIV infection starting HAART
- However, also occurs in normal hosts, especially children, recovering from TB meningitis – "paradoxical tuberculoma"
- With recovery of the immune system, tuberculoma becomes clinically apparent

- Treatment is anti-TB drugs and corticosteroids



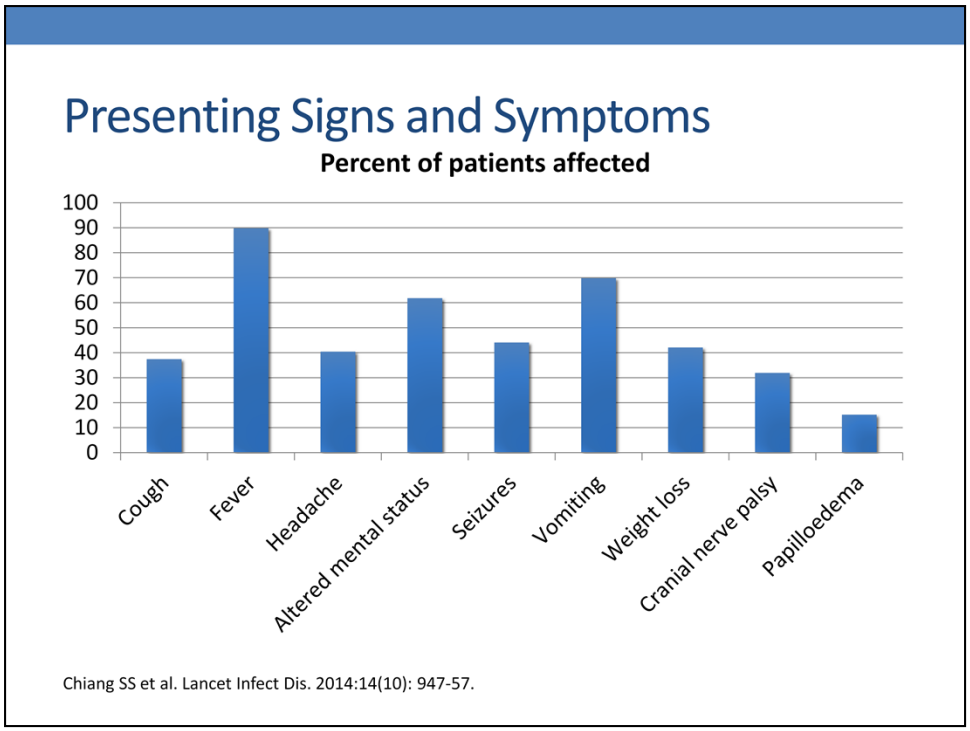
Unlike other forms of bacterial meningitis, TB meningitis presents subacutely, and the patient typically has nonspecific complaints for 1-2 weeks before neurologic signs and symptoms develop.

The disease is divided into 3 stages.

Stage II: vomiting, convulsions, CN palsies, etc.

Stage III: coma, autonomic instability

In the last 10 years, there has been a trend to differentiate stages II and III more objectively, using the Glasgow Coma Scale



The most common signs and symptoms of TB meningitis are nonspecific. In our meta-analysis, we pooled the frequencies of presenting signs and symptoms. The most common was fever, at approximately 90%, followed by vomiting at 70%, and altered mental status at 60%.

There is a caveat to the interpretation of these results: For all of these pooled frequencies, there was significant inter-study heterogeneity, meaning that there was a wide range of frequencies among the different studies.

Diagnostic Evaluation

- Lumbar puncture
  - Cell count, glucose, protein
  - Smear, culture (5-10 mL)
  - NAAT
- Neuroimaging with contrast (MRI preferred)
- Exposure history, contact investigation
- TST/IGRA
- Chest radiograph (PA and lateral)
- +/- gastric aspirates/induced sputum for smear, culture, NAAT
- Serum electrolytes

At a minimum, the evaluation should consist of the following tests . . .

MRI preferred because better for visualizing base of the brain, also better for infarcts

Classic CSF Findings

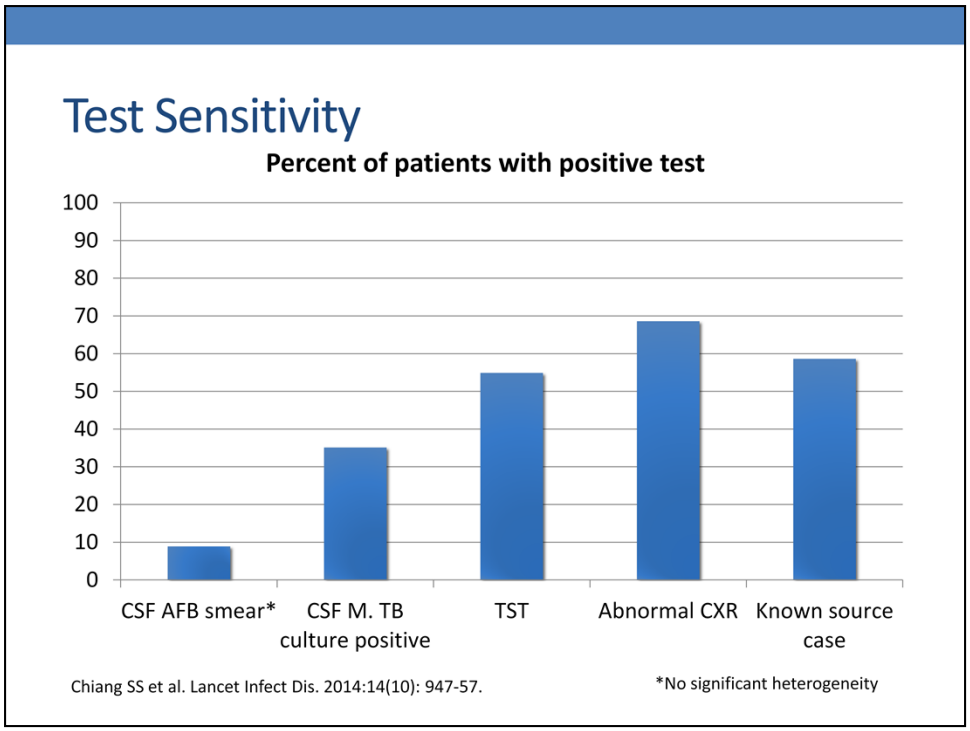
	Bacterial	Viral	TB
Cell count (cells/uL)	5-10,000	0-500	10-500
Cell predominance	Neutrophils	Neutrophils → Lymphocytes	Neutrophils → Lymphocytes
Protein (mg/dL)	20-400	20-60	50-5000
Glucose (mg/dL)	<20	30-80	20-40 (~50% of blood glucose)

CSF findings can provide an important clue to the diagnosis

Cell count is rarely >1000, usually is <500

Protein is typically elevated and can be as high as the 1000s

The glucose is typically low



TBM can be such a difficult disease to diagnose because the tests of microbiologic confirmation are not sensitive . . . It is important to note that there is NOT significant heterogeneity between studies in this pooled frequency of smear positivity. That means that smear positivity was consistently low among the studies we examined.

None of the studies included in our meta-analysis evaluated PCR sensitivity. PCRs are now more widely distributed, and there have been several studies looking at their value in TB meningitis diagnosis. However, the vast majority of study subjects are adults. Nonetheless, extrapolating from the adult data for TB meningitis and from the data looking at PCR use in childhood pulmonary TB, we can guess that PCR sensitivity falls between that of AFB smear and culture (50-70% PCR sensitivity in adults with TB meningitis). The advantage of PCRs is that they result the same day, whereas culture can take up to 6 weeks.

Because microbiologic confirmation is elusive, we have to rely on a battery of other findings to piece together the diagnosis, such as the looking for the typical pattern of CSF cell count, protein, and glucose. In our study population of children with TB meningitis, between 50-60% had a positive TST, nearly 70% had an abnormal CXR (since children w/ TBM often also have pulmonary TB and even miliary TB)

Nucleic Acid Amplification Tests

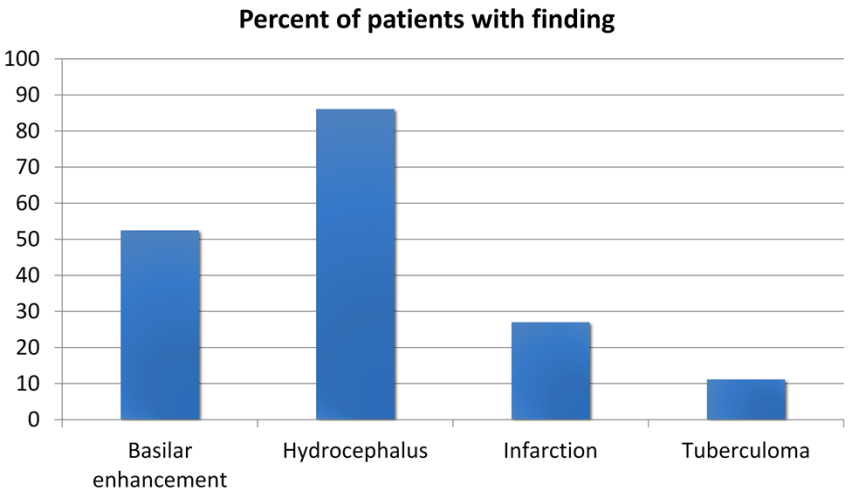
- From India[1]: of 564 CSF
  - 0 smear +
  - 40 Xpert +
- From Italy[2]: of 133 CSF samples
  - 11 culture + Xpert +
  - 2 culture + Xpert –
  - 1 Xpert + culture -
- From South Africa, sensitivities compared to clinical diagnosis (n = 55)[3]:
  - Smear 4% < culture 22% < Xpert 26% < Genotype 33%
  - Smear + culture 22%
  - GenoType + Xpert 49%
  - Culture + GenoType + Xpert 56%

[1]Raizada N et al. PLoS One 2015;10(10): e0140375. doi: 10.1371/journal.pone.0140375
[2]Tortoli E et al. Eur Respir J 2012;40:442-7.
[3]Solomons R et al. Int J Tuberc Lung Dis 2015;19(1):74-80.

2014 WHO Guidance for NTPs on the management of TB in children

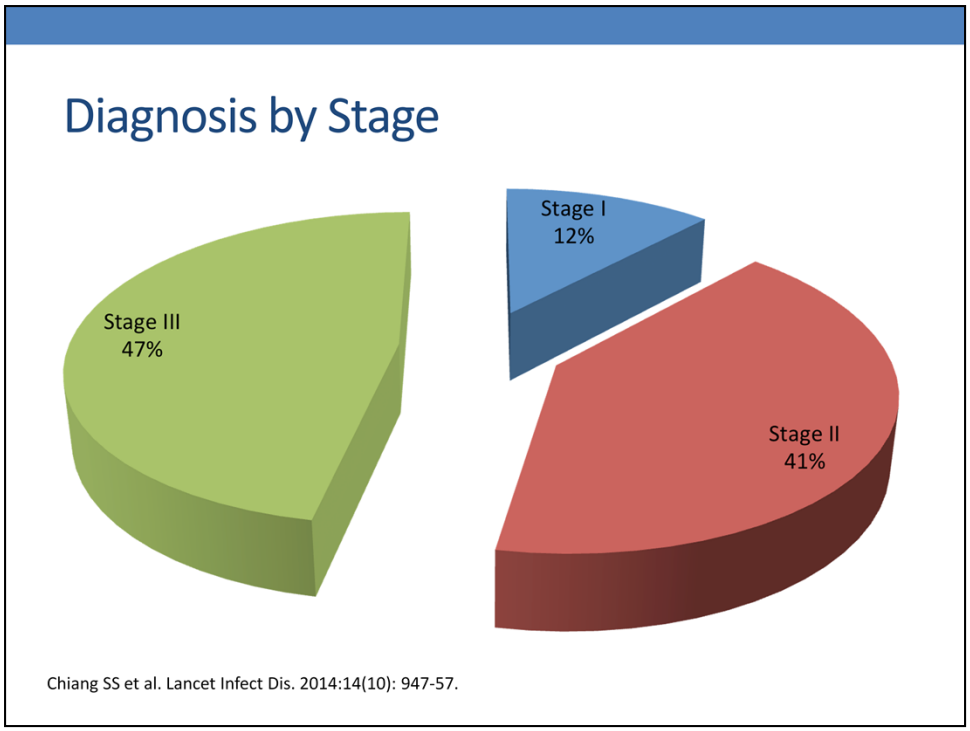
All specificities 98-100%

Neuroimaging Findings

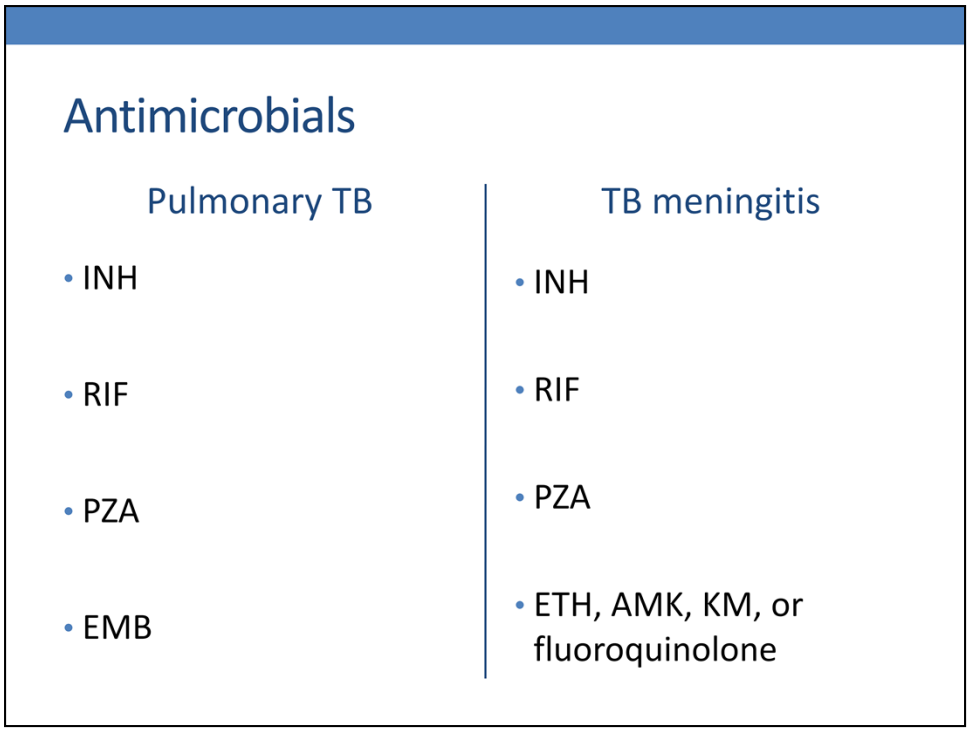


Chiang SS et al. Lancet Infect Dis. 2014:14(10): 947-57.

Vasculitis is also a typical finding in TB meningitis that was not commonly reported



So as you can see, TBM is a difficult diagnosis to make because symptoms and findings are mostly nonspecific and microbiologic confirmation is elusive. It makes sense then that very few patients are diagnosed early. When we looked at the stages in which our study population was diagnosed, we found that the vast majority were diagnosed in stages II or III.



You may already be familiar w/ the 6-month RIPE therapy for pulmonary TB . . . I am going to point out some difference between that regimen and the recommendations for TBM

INH, PZA have excellent CNS penetration—levels in CSF approximate those in serum

RIF concentration in CSF 10-20% of concentration in serum . . . Improved in setting of meningeal inflammation . . . Recent RCT has shown improved outcomes w/ high-dose RIF (IV) in adult TBM (Ruslami R. Lancet Infect Dis 2013.)

EMB *may* penetrate CNS when there is inflammation, has no demonstrated efficacy in TB meningitis

AMK, KM > SM > capreomycin does not penetrate into CNS

Treatment Duration

Pulmonary TB	TB meningitis
• 6 months total	• 9-12 months total
• 2 month intensive	• 2 month intensive
• 4 month continuation	• 7-10 month continuation

Duration depends on individual patient's clinical situation

This recommended regimen is not supported by RCTs . . . BUT it is supported by clinical experience

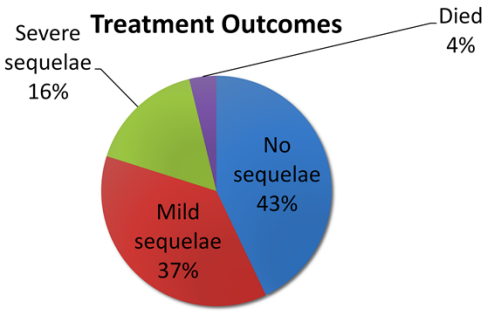
Treatment recommendations are based on clinical experience

Recently there has been RCT in adults comparing treatment regimens that have included high-dose RIF and fluoroquinolones—similar study in children is underway

Observational study in S. Africa of 6 month intensive treatment—good outcomes

Cape Town Regimen

- INH-RIF-PZA-ETH x6 months (x9 months if HIV+)
  - INH 20 mg/kg (max 400 mg)
  - RIF 20 mg/kg (max 600 mg)
  - PZA 40 mg/kg (max 2000 mg)
  - ETH 20 mg/kg (max 750 mg)
  - + steroids



Van Toorn R et al. Pediatr Infect Dis J 2014;33:248-52.

High-dose intravenous rifampin (adults)

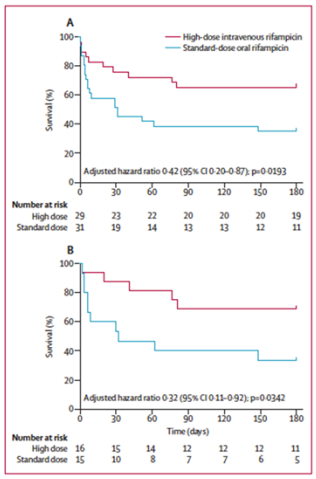


Figure 2: Survival according to rifampicin treatment in all 60 patients (A) and in 31 bacteriologically proven cases of tuberculous meningitis (B)

Ruslami R et al. Lancet Infect Dis. 2014:14(10): 947-57.

High dose = 600 mg (regular = 450)

TBM-KIDS trial (India, Malawi); TBM-KIDS comparing 3 diff intensive phase regimens, followed by standard continuation phase

- HiRIF + INH + PZA + EMB x8 wks
- HiRIF + INH + PZA + LFX x8 wks
- RIF + INH + PZA + EMB x8 wks

Corticosteroids

- Purpose: reduce vasculitis, ICP
- Dose: 2 mg/kg/day prednisone OR dexamethasone 0.3 mg/kg/day x4-6 weeks + taper
- Evidence: shown in RCTs to reduce risk of death in adults and children but do not substantially improve neurological outcomes in survivors[1,2,3]

[1]Prasad K, Singh MB. Cochrane Database Syst Rev. 2008;1: CD002244.
[2]Thwaites GE et al. N Engl J Med. 2004;351: 1741-51.
[3]Schoeman JF et al. Pediatrics 1997;99: 226-31.

Aspirin?

- Purpose: decrease risk of stroke
- Benefit: unclear
  - Shown to be associated w/ reduced risk of stroke in 1 adult RCT (n=118)[1]
  - No difference in outcome in 1 childhood RCT (n=146)[2]
- Not currently recommended

[1]Misra UK et al. J Neurol Sci. 2010;293(1-2): 12-7.
[2]Schoeman JF et al. J Child Neurol. 2011;26(8): 956-62.

Hydrocephalus Management

Mild

- Reduce CSF production: acetazolamide 50 mg/kg/day + furosemide 1 mg/kg/day x 4 weeks

Severe or refractory

- Ventriculostomy or VP shunt
- Shunt placement does not cause peritoneal TB

Acute

- External ventricular drain

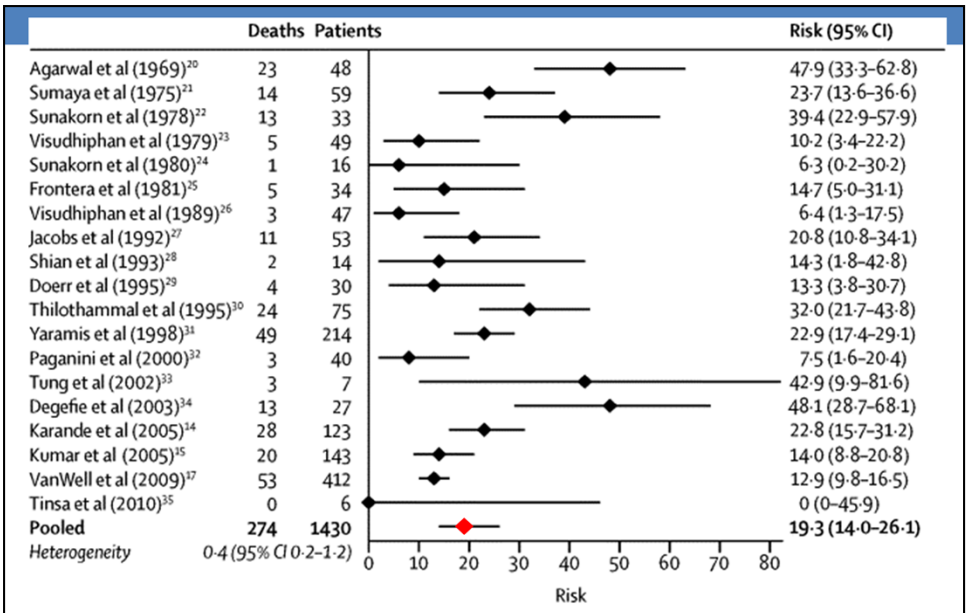
In reality, in industrialized countries, most children w/ TBM and hydrocephalus undergo surgery, but in resource-poor countries where surgery is unavailable or unsafe, there is more reliance on medical management

Surgical intervention decreases pressure immediately but medical intervention does not; no studies comparing the 2

Other Measures

- Fluid/electrolyte management (hypernatremia common)
- Airway protection
- Seizure control
- Physical, occupational, speech therapy

Physical, occupational, speech therapy will be important for a significant percentage of survivors



Death: 19.3% (14.0 – 26.1)

Chiang SS et al. Lancet Infect Dis. 2014:14(10): 947-57.

Neurological Sequelae

More common

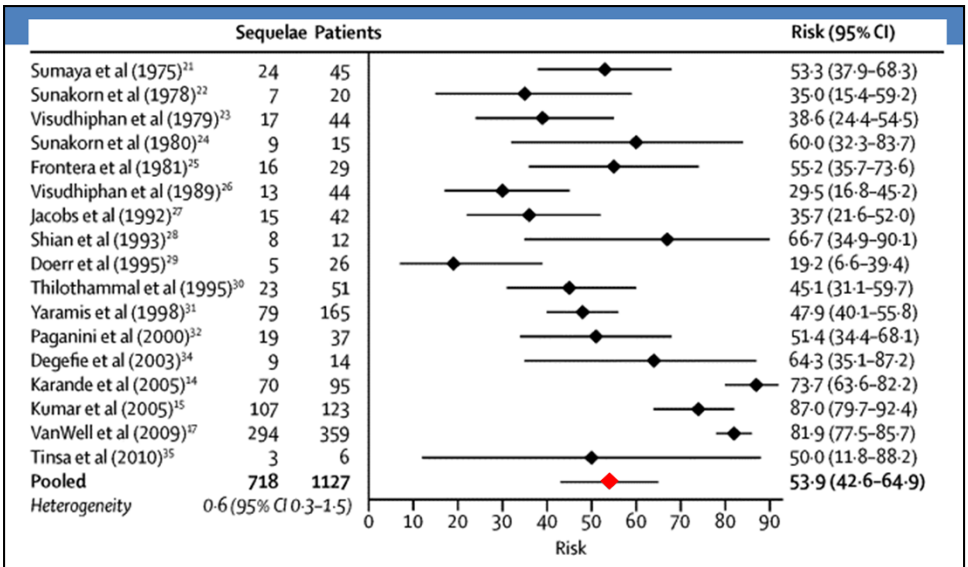
- Developmental delay/intellectual disability
- Behavioral/emotional problems
- Seizures
- Hemiplegia
- Speech/language delay

Less common

- Hearing impairment
- Vision impairment
- Cranial nerve palsy (not II or VIII)
- Quadriplegia
- Diabetes insipidus

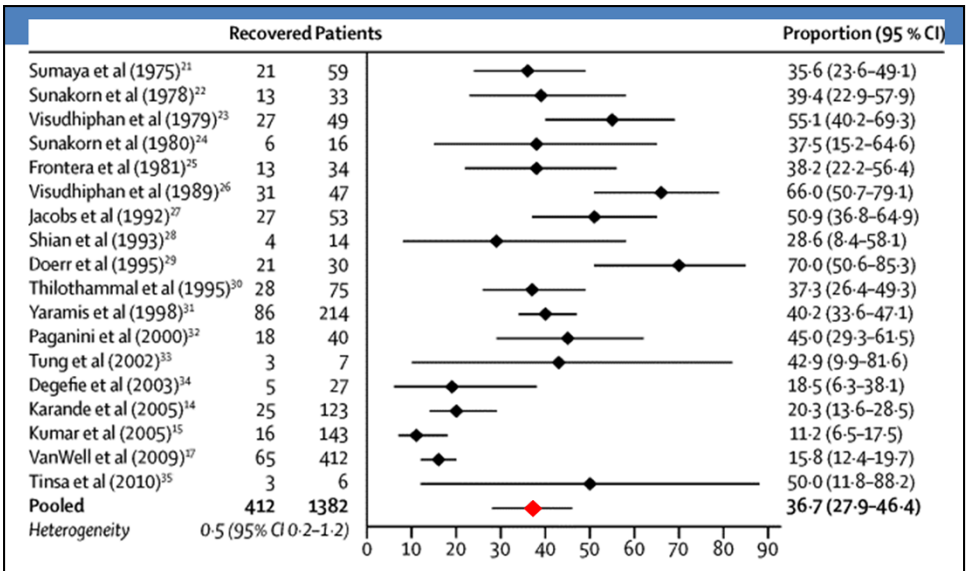
Chiang SS et al. Lancet Infect Dis. 2014:14(10): 947-57.

We also pooled the risk of neurological sequelae.



Neuro sequelae among survivors: 53.9% (42.6 – 64.9)

Chiang SS et al. Lancet Infect Dis. 2014:14(10): 947-57.



Probability of recovery without sequelae: 36.7% (27.9 – 46.4)

Chiang SS et al. Lancet Infect Dis. 2014:14(10): 947-57.

Sources of Heterogeneity?

- Study setting: GDP, era
- Patient characteristics: age, sex, BCG vaccination status
- Treatment characteristics: receipt of certain antibiotics, doses of certain antibiotics, number of antibiotics, use of steroids, length of treatment

No individual patient data—looked at study-level outcomes

Drug resistance data limited

Sources of Heterogeneity?

Bottom line:

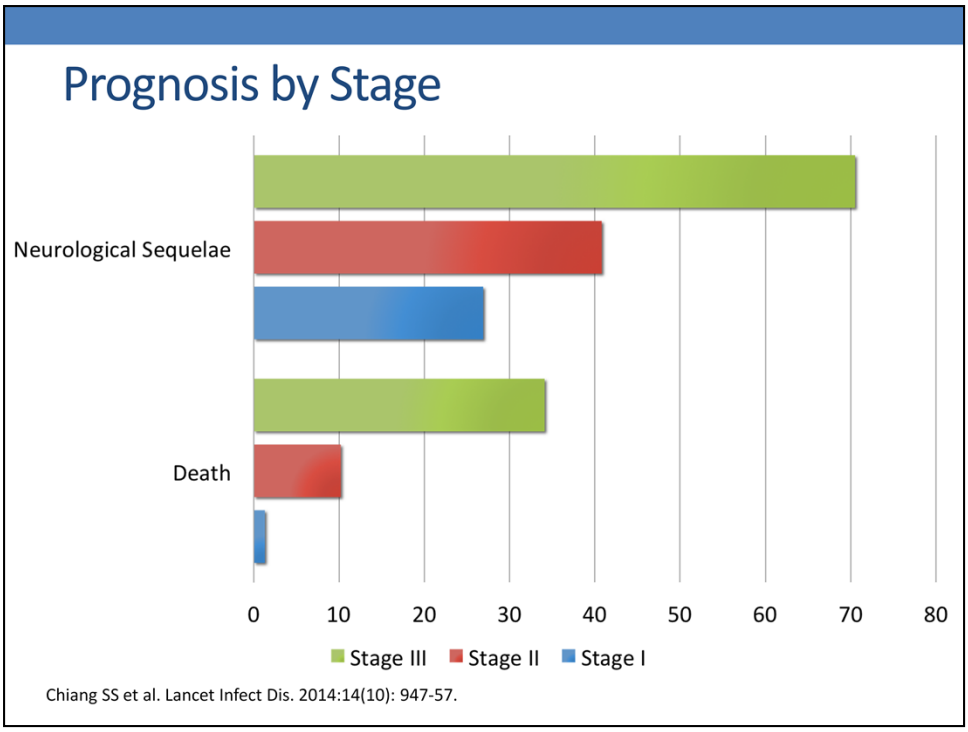
We did not identify any study setting, patient, or treatment characteristics associated with outcomes

Caveats:

- Study-level, not individual patient-level analysis
- Univariable, not multivariable meta-regression

Also, GDP, era were not associated w/ outcomes—interestingly, outcomes have not improved over the past 50 years

Not contradicting importance of corticosteroid use



I would like to point out that while there was significant heterogeneity in our pooled risks of death and neurological sequelae for all patients put together, when we stratified patients by stage, the heterogeneity disappeared for stages I and II.

Taken together with the fact that most childhood TB meningitis cases are diagnosed in stage II or III, and how difficult it is to diagnose the disease in stage I, these outcomes mean that prevention is of crucial importance.

Prevention

BCG Vaccine

- BCG is 60-70% effective in preventing TB meningitis in 1st 5 years[1]
- Half of 22 high-burden countries reported vaccination rates 47-85% in 2011[2]

Contact Investigation/Therapy for Infection

- Evidence of INH efficacy has existed >50 years
- Rarely implemented in high-burden, resource-limited areas
- Limitation: child w/ TB meningitis is often index case

[1]Colditz GA et al. Pediatrics 1995;96: 29-35.
[2]Graham SM and Donald PR. Lancet Infect Dis. 2014;14(10): 902-4.

Preventive strategies that are known to work are not being optimized.

BUT contact investigation solidifies diagnosis

Remaining Knowledge Gaps

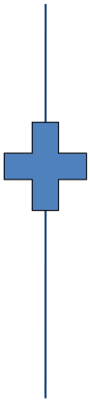
- Best method for lowering intracranial pressure
- Best initial regimen, including role of FQs
- Value of ASA and other adjunctive therapies
- More effective vaccines

Summary

- Overall outcomes are poor but are better with early diagnosis
- Early diagnosis is elusive because microbiologic tests have low sensitivity and early presentation is nonspecific
- Preventive measures are essential: BCG, contact investigation, isoniazid therapy
- In the appropriate context, clinicians must maintain high index of suspicion and low threshold for empiric therapy w/o waiting for confirmation

Clinical Implication

- Basilar exudate
- Cranial nerve involvement
- Hydrocephalus
- Vasculitis
- Ischemic > hemorrhagic infarction
- Tuberculoma



No other obvious etiology identified

DO NOT DELAY!!! START TB TREATMENT WHILE EVALUATION IN PROGRESS

If a child has meningitis, no obvious cause, any of the following features: CN involvement, basilar enhancement, evidence of vasculitis or stroke, hydrocephalus . . . They should be started on TB therapy while you are trying to figure out the actual cause