Meningeal Tuberculosis (Tuberculous Meningitis) — Comprehensive Disease Characterization Report

Target Disease: Meningeal tuberculosis / Tuberculous meningitis (TBM) **MONDO ID:** MONDO:0006042 **Category:** Infectious Disease **Report basis:** 15 confirmed findings, 68 papers reviewed across 5 investigation iterations

Summary

Meningeal tuberculosis (tuberculous meningitis, TBM) is the most lethal and disabling form of tuberculosis, arising when *Mycobacterium tuberculosis* infects the meninges and subarachnoid space of the central nervous system. It is fundamentally an **infectious disease with a strong immunopathological component**: the initiating lesion is a subpial or subependymal caseous granuloma (the **Rich focus**) that ruptures into the subarachnoid space, seeding a dense basal meningeal exudate. This exudate drives the three cardinal complications that define the disease's morbidity and mortality — **vasculitis with cerebral infarction, hydrocephalus, and cranial neuropathy** — together with blood-brain-barrier (BBB) breakdown mediated by matrix metalloproteinase-9 (MMP-9) (PMID: 7610242; PMID: 19789647).

TBM accounts for roughly 1% of all active TB cases (1–5% of TB, ~14% of all meningitis) but carries an in-hospital mortality near 42%, rising toward 70% in HIV co-infection, and left ~78,200 adults dead in 2019 alone (PMID: 35288778; PMID: 36795648). Survivors frequently suffer multidomain cognitive impairment and focal neurological deficits. Diagnosis remains a central challenge because no single test is both sensitive and specific: clinicians rely on a composite of CSF findings (lymphocytic pleocytosis, elevated protein, low glucose, elevated adenosine deaminase), molecular testing (Xpert MTB/RIF Ultra, ~77% sensitive), and the neuroimaging triad of basal meningeal enhancement, hydrocephalus, and basal-ganglia infarction (PMID: 31924549; PMID: 28281443).

Treatment is prolonged multidrug antituberculous therapy — the WHO-standard 12-month HRZE-based regimen (2HRZE/10HR) — because standard 6-month pulmonary regimens penetrate the CNS poorly. Adjunctive corticosteroids are standard, but their survival benefit is now understood to be **host-genotype-dependent**: leukotriene A4 hydrolase (*LTA4H*) promoter genotype defines hyper-, intermediate-, and low-inflammatory phenotypes, and the phase 3 LAST ACT trial found no dexamethasone benefit in the CC/CT (lower-inflammation) genotypes (PMID: 41540106). Prevention rests principally on neonatal BCG vaccination, which is ~90% protective against the meningeal and miliary childhood forms (PMID: 24336911).

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1. Disease Information

Overview. TBM is a subacute-to-chronic granulomatous meningitis caused by *Mycobacterium tuberculosis* reaching the CNS, usually via hematogenous dissemination from a primary (typically pulmonary) focus. It is the most severe manifestation of extrapulmonary TB. Untreated, it "presents as a subacute to chronic meningitis syndrome with a prodrome of malaise, fever, and headache progressing to altered mentation and focal neurologic signs, followed by stupor, coma, and death within five to eight weeks of onset" (PMID: 28281443).

Key identifiers: | Resource | Identifier | |---|---| | MONDO | MONDO:0006042 | | MeSH | Tuberculosis, Meningeal (D014390) | | ICD-10 | A17.0 (Tuberculous meningitis) | | ICD-11 | 1B41 (Tuberculosis of the nervous system) | | SNOMED CT | Tuberculous meningitis (disorder) |

Synonyms / alternative names: tuberculous meningitis, TB meningitis, TBM, meningeal tuberculosis, tuberculosis of the meninges, CNS tuberculosis (broader — includes tuberculoma and spinal arachnoiditis).

Information source type. This report aggregates **disease-level** evidence from systematic reviews, meta-analyses, randomized controlled trials, and cohort studies, supplemented by mechanistic model-organism and in-vitro work. It is not derived from individual EHR records.

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2. Etiology

Primary cause (infectious). TBM is caused by *Mycobacterium tuberculosis* (NCBI Taxonomy 1773; complex 77643). The mechanistic trigger is the **Rich focus** — a caseating granuloma seeded during bacillemia that lodges subpially/subependymally and later ruptures into the subarachnoid space (PMID: 7610242).

Genetic risk factors (host susceptibility). Susceptibility and severity are shaped by host genetic polymorphisms and by pathogen lineage. "Pathogen lineage (Beijing genotype) and host genetics (polymorphisms in TLR2, TIRAP and LTA4H genes) can influence susceptibility to TBM" (PMID: 22953709). The *LTA4H* (leukotriene A4 hydrolase; HGNC:6710) promoter genotype is the best-characterized modifier, defining three intracerebral inflammatory phenotypes: **TT (hyperinflammatory), CT (intermediate), CC (low inflammation)** (PMID: 41540106).

Environmental / demographic risk factors. HIV co-infection is the dominant risk factor and outcome modifier. Other risks include young age (children <5 years present with more advanced disease), high community TB burden, low Human Development Index, malnutrition, and lack of BCG vaccination (PMID: 36795648; PMID: 41639788).

Protective factors. Neonatal BCG vaccination is strongly protective against meningeal/miliary TB (~90%) (PMID: 24336911). No robustly validated protective human genetic variant is established for TBM specifically.

Gene-environment interaction. The clearest GxE relationship is *LTA4H* genotype × corticosteroid therapy: the anti-inflammatory (steroid) intervention interacts with the host inflammatory set-point, so benefit is expected in the hyperinflammatory TT genotype but is uncertain/absent in CC/CT (PMID: 41540106; PMID: 22304914).

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3. Phenotypes

TBM produces symptoms/signs (clinical), physical manifestations, behavioral/cognitive change, and laboratory abnormalities. Onset is subacute (typically days-to-weeks). Frequencies below are drawn from cohort and review data.

Phenotype	Type	Frequency / notes	Suggested HPO
Fever	Symptom	~67–80%	HP:0001945
Headache	Symptom	~33–63%	HP:0002315
Vomiting / nausea	Symptom	~52–92% (children higher)	HP:0002013
Altered mental status / consciousness	Sign	~55–78%	HP:0011446
Meningismus / nuchal rigidity	Sign	~38% +	HP:0002829
Seizures	Sign	~72% (children)	HP:0001250
Cranial neuropathy (e.g., optic, oculomotor)	Sign	common (basal exudate entrapment)	HP:0000496
Focal deficit / hemiparesis (stroke)	Sign	~30% (stroke)	HP:0001269
Hydrocephalus	Manifestation	26–63% imaging	HP:0000238
Cognitive impairment (memory, attention, executive)	Behavioral/ cognitive	12–>90% survivors	HP:0100543
Lymphocytic CSF pleocytosis	Lab	classic	HP:0012229 (abnormal CSF)
Hyponatremia	Lab	~46–93%	HP:0002902

Characteristics. Onset spans neonatal through geriatric, with a pediatric predilection for severe meningoencephalitis. Severity is graded by the British Medical Research Council (BMRC) stages I–III. Progression is typically progressive if untreated. Cognitive sequelae "most consistently affected memory, attention, and executive function" (PMID: 41629635). Younger children carry a disproportionate burden: "The < 5 years group had a higher proportion of TBM stage III cases (29.5% vs. 2.2%, p <0.001)" (PMID: 41639788).

Quality of life. Survivors face substantial disability from motor deficits, epilepsy, hydrocephalus-related morbidity, and cognitive dysfunction spanning mild deficits to severe global dysfunction (PMID: 41629635).

4. Genetic / Molecular Information

TBM is **not a Mendelian genetic disease** — there are no causal genes, pathogenic ACMG-classified variants, chromosomal abnormalities, or germline/somatic driver mutations. Host genetics act as **susceptibility/modifier factors**, not as causes:

- ***LTA4H*** (HGNC:6710) — promoter polymorphism defines inflammatory phenotype and modifies corticosteroid response (PMID: 41540106).
- ***TLR2*** (Toll-like receptor 2) and ***TIRAP*** (TIR domain adaptor) — susceptibility polymorphisms (PMID: 22953709).

Epigenetic information: No TBM-specific human epigenomic signature is established in the reviewed literature.

The relevant "molecular" pathology is therefore host-inflammatory rather than genomic. The *LTA4H*-encoded enzyme sits at the eicosanoid branch point governing the balance of pro-inflammatory leukotriene B4 versus anti-inflammatory lipoxins (PMID: 22304914).

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5. Environmental Information

- **Infectious agent:** *Mycobacterium tuberculosis* (NCBI Taxon 1773); the **Beijing lineage** is associated with increased TBM susceptibility (PMID: 22953709). CHEBI-relevant host mediators include leukotriene B4 (CHEBI:15514) and lipoxins.
- **Environmental/lifestyle contributors:** crowding and airborne transmission of TB, malnutrition, immunosuppression (notably HIV), and absence of BCG vaccination. HIV co-infection modifies presentation — persons living with HIV "exhibited lower frequencies of vomiting, nuchal rigidity, signs of meningeal inflammation, and coma, along with lower leukocyte counts in cerebrospinal fluid" (PMID: 40589807).

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6. Mechanism / Pathophysiology

Ordered causal chain (initiating lesion → clinical manifestation)

1. **Inhalation of *M. tuberculosis*** → primary (usually pulmonary) infection → hematogenous dissemination **leads to** seeding of subpial/subependymal caseous granulomas (**Rich foci**). *(Demonstrated — classic neuropathology.)*
2. **Rupture of a Rich focus** into the subarachnoid space **results in** release of bacilli and antigen into CSF (PMID: 7610242).
3. Antigen release **triggers** a dense **basal meningeal exudate** of mononuclear/epithelioid cells and Langhans giant cells around the basal cisterns (PMID: 7610242).
4. The exudate **branches** into three parallel injury pathways:
5. **(4a) Vasculitis branch:** exudate encases perforating arteries → arteritis → "arteritic occlusion of larger arteries, such as the middle cerebral" → **infarction**, characteristically in the basal ganglia (lateral striate, MCA, medial striate territory) (PMID: 7610242; PMID: 36048445).
6. **(4b) CSF-flow branch:** "Blockage of the basal subarachnoid cisterns ... or narrowing of aqueduct and third ventricle by a small tuberculoma causes consequent **hydrocephalus**" (PMID: 7610242).
7. **(4c) Cranial-nerve branch:** entrapment of optic nerves and other cranial nerves in the interpeduncular fossa → **cranial neuropathies** (PMID: 7610242).
8. **In parallel**, neutrophil-driven and macrophage-driven secretion of **MMP-9** (a zinc-dependent gelatinase) **degrades basement membrane/extracellular matrix → blood-brain-barrier disruption** and neuroinflammatory injury (PMID: 19789647; PMID: 39536643).
9. Host **inflammatory set-point (LTA4H genotype)** modulates the magnitude of steps 3–5: both inadequate and excessive inflammation converge on **dysregulated TNF**, worsening outcome (*inferred from zebrafish/human correlation*) (PMID: 22304914).
10. Combined ischemia, hydrocephalus, BBB breakdown and edema **result in** raised intracranial pressure, coma, and death, or — in survivors — cognitive and focal neurological sequelae (PMID: 41629635).

Detail by category

Cellular / immune processes. Granulomatous inflammation (epithelioid macrophages, Langhans giant cells, lymphocytes) is the dominant tissue response (PMID: 7610242). Early pathogenesis has a neutrophilic component: "The strong correlation between CSF MMP-9 and neutrophil count suggests that polymorphonuclear leukocytes may play a central role in the early pathogenesis of TBM" (PMID: 19789647). Specialized pro-resolving mediators (resolvins, lipoxins) decline with severity, and their CSF concentrations associate with 80-day survival (PMID: 31500466).

Protein dysfunction / biochemical abnormality. MMP-9 over-activity is central to matrix destruction. In a mouse CNS-TB model, SHH-pathway antagonism "upregulated Matrix Metalloproteinase-9 (MMP-9) secretion, a key contributor to BBB disruption," severe gliosis, and a 99% increase in brain bacillary load (PMID: 39536643). Dexamethasone "significantly reduced CSF MMP-9 concentrations in early follow up samples" (PMID: 19789647).

Molecular pathway. The eicosanoid/LTA4H axis (leukotriene B4 vs lipoxin balance) tunes TNF signaling: "inadequate inflammation caused by excess lipoxins and hyperinflammation driven by excess leukotriene B(4)" both cause susceptibility (PMID: 22304914). The sonic hedgehog (SHH) pathway is implicated in BBB integrity (PMID: 39536643).

Suggested ontology terms. GO: inflammatory response (GO:0006954), extracellular matrix disassembly (GO:0022617), blood-brain barrier maintenance (GO:0035633), leukotriene metabolic process (GO:0006691). CL: macrophage (CL:0000235), epithelioid cell, Langhans giant cell, neutrophil (CL:0000775), T lymphocyte (CL:0000084).

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7. Anatomical Structures Affected

Organ / system level. Primary organ: **brain and meninges** (nervous system). The basal meninges, subarachnoid cisterns, and CSF pathways are the epicenter. Secondary involvement: cerebral parenchyma (infarcts, tuberculomas, encephalitis), ventricular system (hydrocephalus), cranial nerves, and spinal cord/arachnoid (spinal arachnoiditis). Systemic dissemination (miliary TB) is common in children.

Vascular territory. Basal-ganglia perforators are characteristically affected: "The lateral striate, middle cerebral, and medial striate arteries were typically affected" — the perforator "TB zone" encased by exudate (PMID: 36048445).

Tissue / cell level. Leptomeninges (pia-arachnoid), cerebral arterial walls (arteritis), ependyma, and choroid/aqueductal structures. Cell populations: macrophages, epithelioid and Langhans giant cells, lymphocytes, neutrophils.

Localization / UBERON: meninges (UBERON:0002360), leptomeninges/subarachnoid space (UBERON:0002450), basal cistern, brain (UBERON:0000955), cerebrospinal fluid (UBERON:0001359), middle cerebral artery (UBERON:0001627), basal ganglia (UBERON:0002420), cerebral ventricle (UBERON:0002285). Lateralization is typically **bilateral/basal** but infarcts may be focal/asymmetric.

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8. Temporal Development

- **Onset:** any age, with pediatric predilection; onset is **subacute to chronic** (prodrome of days to weeks).
- **Staging:** BMRC grades I (alert, no deficit), II (altered consciousness/focal signs), III (stupor/coma, dense deficit). Advanced stage predicts poor outcome — up to 100% fatality in stage III in one pediatric series (PMID: 41288109).
- **Untreated course:** progression from "malaise, fever, and headache progressing to altered mentation and focal neurologic signs, followed by stupor, coma, and death within five to eight weeks of onset" (PMID: 28281443).
- **Treated course:** prolonged (≥12 months therapy); paradoxical reactions may occur during treatment in ~21% of CNS-TB (PMID: 42242389).
- **Critical period:** early diagnosis and treatment initiation is the key intervention window; delay strongly worsens outcome.

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9. Inheritance and Population (Epidemiology)

- **Proportion of TB:** "Tuberculosis meningitis (TBM) accounts for approximately 1% of all active TB cases" (1–5% of TB) (PMID: 36795648).
- **Prevalence:** CNS-TB ~2 per 100,000 inhabitants; represents "13.91% of all cases of meningitis and 4.55% of all cases of TB" (PMID: 35288778).

- **Mortality:** in-hospital mortality "rose up to 42.12% in hospitalized patients" (PMID: 35288778); ~40% HIV-negative, up to ~70% with HIV. In 2019, "78,200 adults died of TB meningitis" (PMID: 36795648). An estimated 24,000 children <15 years developed TBM in 2019, of whom ~16,100 died (PMID: 39706662).
- **Inheritance:** Not applicable (infectious disease). Host susceptibility is **multifactorial/ polygenic** (TLR2, TIRAP, LTA4H).
- **Geographic distribution:** burden concentrated in high-TB-incidence, low-HDI settings and areas of high HIV prevalence.
- **Demographics:** male predominance in many cohorts; younger children over-represented among severe cases.

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10. Diagnostics

No single test reliably rules TBM in or out; diagnosis is a composite.

CSF profile. "Cerebrospinal fluid (CSF) analysis showed lymphocytic pleocytosis, elevated protein, low glucose levels, and cobweb coagulum indicative of TBM" (PMID: 37915698).

Adenosine deaminase (ADA). A useful adjunct with high specificity but limited sensitivity: "ADA was the best performing parameter. It attained a specificity of 95%, a positive likelihood ratio of 10.7, and an area under the receiver operating characteristics curve of 82.1%, but had a low sensitivity (55%)" (PMID: 23973430).

Molecular tests. Xpert MTB/RIF Ultra is the WHO first-choice test: "Xpert Ultra had 76·5% sensitivity (95% CI 62·5-87·2 ...) and a negative predictive value of 92·7%," superior to Xpert (~56%) and MGIT culture (~61%) (PMID: 31924549). Metagenomic NGS reaches ~84% sensitivity and CSF pyrosequencing higher still, but "mNGS cannot be used as a rule-out test" (PMID: 35202495).

Culture. Confirmatory but insensitive: "The overall pooled estimates of CSF culture positive TBM was 29.72%" (PMID: 36795648).

Drug-resistance testing. Targeted NGS on CSF (e.g., Deeplex Myc-TB) enables rapid resistance detection: "Targeted next-generation sequencing (tNGS) produces high read depths, allowing the detection of DR-associated alleles with low frequencies" (PMID: 38466092).

Neuroimaging. The **TBM triad** — basal meningeal enhancement + hydrocephalus + basal-ganglia infarction — is diagnostically valuable: "the combination of meningeal enhancement and any degree of hydrocephalus is strongly suggestive of TBM" (PMID: 28281443). In a 559-case series: tuberculomas 40%, basal meningeal enhancement 41%, infarction 27%, hydrocephalus 26% (PMID: 31115112).

Test	Sensitivity	Specificity/NPV	Source
CSF Xpert Ultra	~77%	NPV 92.7%	P 31924549
CSF Xpert (original)	~56%	—	P 31924549
MGIT culture	~25–61%	culture-positive ~30%	P 36795648
CSF mNGS	~84%	not rule-out	P 35202495
CSF pyrosequencing	~98%	NPV ~98%	P 33421910
CSF ADA	~55%	~95% spec	P 23973430

Clinical criteria. The Marais/uniform case definition (definite/probable/possible) and Thwaites score are used to classify cases. **Differential diagnosis** includes cryptococcal meningitis, bacterial/partially-treated bacterial meningitis, viral meningoencephalitis, carcinomatous meningitis, and neurosarcoidosis (PMID: 41788392).

11. Outcome / Prognosis

- **Mortality:** ~40% overall (HIV-negative), up to ~70% with HIV co-infection; in-hospital ~42% (PMID: 35288778).
- **Morbidity:** high rates of long-term neurological and cognitive sequelae. "Cognitive impairment ranging from 12% to over 90% was found across studies ... The most consistently affected domains were memory, attention, and executive function" (PMID: 41629635).

- **Complications:** stroke/infarction (~30%), hydrocephalus, seizures/epilepsy, cranial neuropathies, hyponatremia, paradoxical reactions, IRIS (in HIV).
- **Prognostic factors:** BMRC stage at presentation (dominant), age (<5 years worse), HIV status, drug resistance, hyponatremia severity/persistence, low albumin/hemoglobin, delayed treatment. "Persistent hyponatraemia and increasing urinary output during treatment associate with worse clinical out[come]" (PMID: 42167495).
- **Stroke burden:** "The frequency of stroke in TBM showed an estimate of 0.30 (95% CI, 0.26-0.33)" (PMID: 36048445).

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12. Treatment

Standard antituberculous therapy. WHO recommends **12 months** of therapy for TBM: "the World Health Organization recommends 12 months of treatment for TBM. The drugs used in the treatment are rifampicin, isoniazid, ethambutol, and pyrazinamide" (regimen 2HRZE/10HR) (PMID: 39752122). CNS penetration differs by drug: "pyrazinamide penetrates the brain better than other drugs and kills TB bacteria more effectively. In addition, ethambutol does not get into the brain" (PMID: 39752122). Rifampicin CNS penetration is limited, motivating high-dose (25–35 mg/kg) trials (PMID: 34494572). Suggested NCIT terms: Isoniazid (C557), Rifampicin/Rifampin (C608), Pyrazinamide (C777), Ethambutol (C486), Dexamethasone (C405).

Pediatric intensified regimen. A 6-month intensified regimen (higher-dose H/R, pyrazinamide, ethionamide replacing ethambutol; 6HRZEto) markedly improved outcomes: "death, 5.5% ... vs 23.9% ...; treatment success (survival with or without sequelae), 94.6% ... vs 75.4%" (PMID: 35673608).

Adjunctive corticosteroids (NCIT: dexamethasone, prednisolone). Standard of care for HIV-negative adults and children — but benefit is host-genotype-dependent. In the phase 3 LAST ACT trial (HIV-negative, CC/CT genotypes), "the primary endpoint of all-cause death or new neurological event over 12 months from randomization occurred in 108/305 (35.4%) given dexamethasone and 110/308 (35.7%) given placebo (hazard ratio of 0.99)" — i.e., no benefit in lower-inflammation genotypes (PMID: 41540106). In HIV-positive adults, adjunctive dexamethasone "did not confer a benefit with respect to survival" (PMID: 37819954).

Host-directed / adjunctive therapy. Aspirin, high-dose rifampicin, and linezolid are under trial (LASER-TBM, INTENSE-TBM, INSHORT, SURE). MMP inhibition (e.g., doxycycline) is a preclinical host-directed strategy (PMID: 41819159).

HIV co-management. ART improves survival but timing is critical — early ART increases IRIS/adverse events in TBM; prednisone "is effective in both preventing and treating the paradoxical tuberculosis-associated immune reconstitution inflammatory syndrome" (PMID: 31272663).

Supportive / surgical. Management of hydrocephalus (CSF diversion/shunting), seizure control, hyponatremia correction (distinguishing SIADH from cerebral salt wasting, which require opposite fluid strategies), and rehabilitation.

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13. Prevention

- **Primary — BCG vaccination.** The cornerstone. "Protection against meningeal and miliary tuberculosis was also high in infants (RR, 0.1; 95% CI, .01-.77)" — ~90% efficacy (PMID: 24336911). "the neonatal Bacillus Calmette-Guérin (BCG) is the only vaccine against TB and offers significant efficacy against disseminated and meningeal disease in children" (PMID: 40498907). Protection against pulmonary TB is weaker and more variable.
- **Secondary.** Early case detection and prompt treatment initiation; TB preventive therapy in high-risk (e.g., HIV) individuals; contact tracing.
- **Tertiary.** Corticosteroids to limit inflammatory injury (genotype-informed), hydrocephalus management, and prevention/treatment of IRIS.
- **Public health.** TB control programs, HIV control, nutrition, and reduction of transmission.

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14. Other Species / Natural Disease

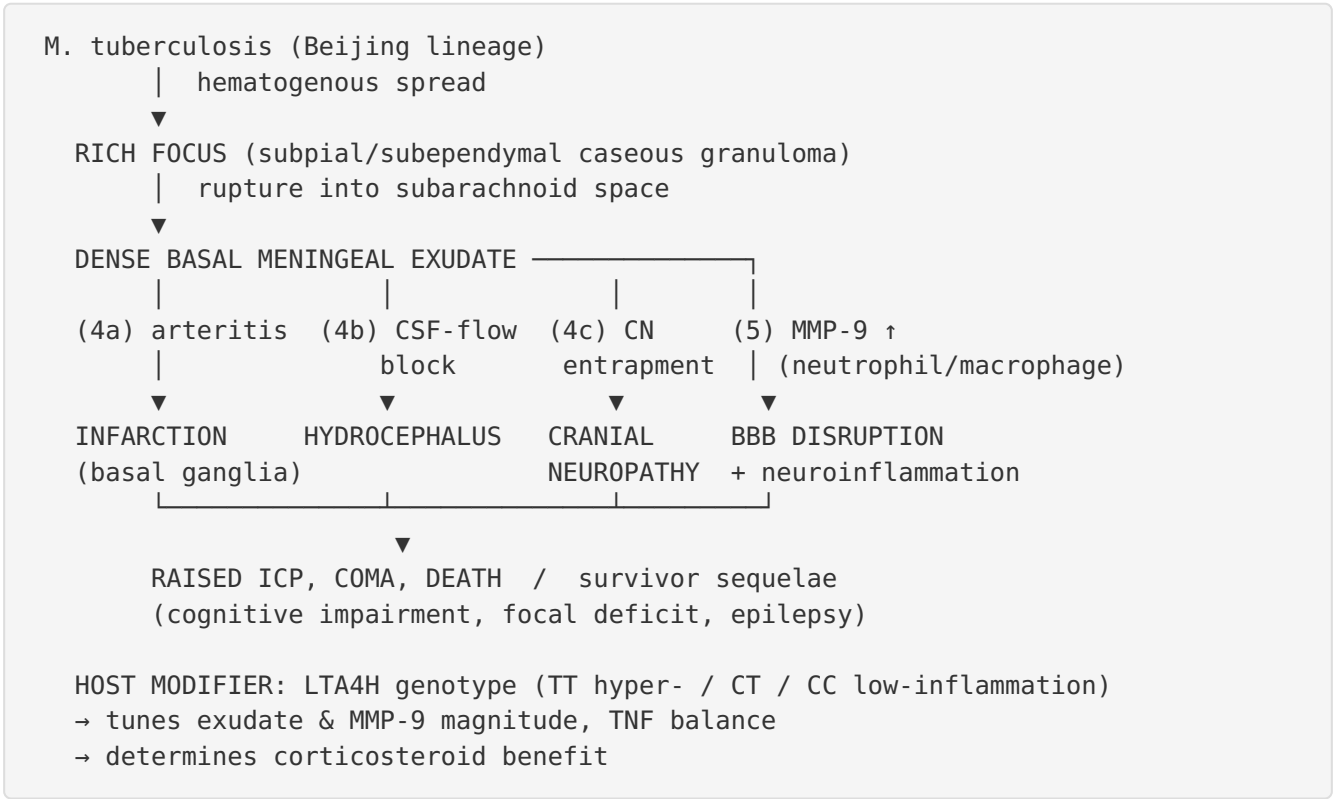
TBM is fundamentally a human disease. *M. tuberculosis* has limited natural host range, though *M. bovis* (zoonotic) can cause CNS TB. Experimental infection with *Mycobacterium marinum* in zebrafish reproduces key inflammatory susceptibility biology (PMID: 22304914). Zoonotic potential exists for bovine TB. No dedicated companion-animal natural-TBM literature was identified in this review.

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15. Model Organisms

- **Zebrafish (*Danio rerio*) / *M. marinum*.** Establishes the "inverted-U" inflammation model: "susceptibility to Mycobacterium marinum can result from either inadequate or excessive acute inflammation," driven by the LTA4H eicosanoid balance; the human LTA4H polymorphism "is associated with inflammatory cell recruitment, patient survival and response to adjunctive anti-inflammatory therapy" (PMID: 22304914). **Strength:** models host-genotype-directed therapy. **Limitation:** does not reproduce full basal-exudate neuropathology.
- **Mouse CNS-TB model.** SHH-modulated rapid CNS-TB model recapitulates MMP-9-driven BBB breakdown, reactive gliosis, and increased brain bacillary load (PMID: 39536643). **Application:** BBB pathology and drug/host-directed therapy discovery.

Mechanistic Model / Interpretation



The disease is best understood as a **two-hit process**: (1) the mechanical/infectious hit of the Rich focus rupturing and generating a strategically located basal exudate, and (2) the immunopathological hit of dysregulated host inflammation (eicosanoid/TNF imbalance, MMP-9-mediated matrix destruction). The exudate's anatomical location — around the basal cisterns and perforating arteries — explains why the three cardinal complications are stereotyped (basal-ganglia stroke, obstructive hydrocephalus, cranial neuropathy). The host-inflammatory hit explains why anti-inflammatory adjunctive therapy helps some patients (hyperinflammatory TT) but not others (CC/CT), and why both too little and too much inflammation are harmful.

Evidence Base

PMID	Contribution
7610242	*Neuropathology* — establishes Rich focus → basal exudate → vasculitis/hydrocephalus/ CN entrapment chain
22953709	Host (TLR2, TIRAP, LTA4H) and pathogen (Beijing) susceptibility factors
41540106	LAST ACT phase 3 — genotype-stratified dexamethasone; null in CC/CT
22304914	Zebrafish LTA4H inverted-U inflammation model; links to human steroid response
19789647	Dexamethasone lowers CSF MMP-9; MMP-9/neutrophil link
39536643	Mouse model — MMP-9 drives BBB disruption
31924549	Xpert Ultra diagnostic performance (~77%)
23973430	CSF ADA performance (spec 95%, sens 55%)
35288778	Epidemiology & mortality meta-analysis
36795648	Microbiological diagnosis & mortality; 78,200 adult deaths (2019)
36048445	Stroke frequency (~30%) and vascular territory
41629635	Cognitive sequelae meta-analysis
35673608	Pediatric 6-month intensified regimen outcomes
39752122	WHO 12-month regimen & CNS drug penetration
42167495	Hyponatremia prevalence & prognostic value
34510291	SIADH vs cerebral salt wasting frequencies
24336911	BCG ~90% protection vs meningeal/miliary TB
28281443	Untreated temporal course; imaging triad value
31115112	Imaging finding frequencies (559 cases)
38466092	tNGS for rapid CSF drug-resistance detection
37819954	Dexamethasone no benefit in HIV-positive adults
42242389	Paradoxical reactions (~21%) in CNS-TB

Limitations and Knowledge Gaps

1. **Diagnostic gap.** No test reliably excludes TBM; culture confirms only ~30%, and even Xpert Ultra misses ~1 in 4 cases. Delayed diagnosis remains a leading cause of death.
2. **Corticosteroid uncertainty.** The genotype-stratified null result in CC/CT and the HIV-positive null challenge decades of blanket steroid use; optimal, genotype-informed anti-inflammatory strategy is unresolved.
3. **Drug penetration.** Standard regimens penetrate the CNS poorly; optimal doses of rifampicin/linezolid and duration are still under trial.
4. **Host-directed therapy.** MMP-9 inhibition, aspirin, and resolvin biology are promising but not yet standard.
5. **Pediatric/HIV evidence.** Much mechanistic and trial data derive from adult, HIV-negative Vietnamese cohorts; generalizability to children and HIV-endemic African settings is incomplete.
6. **No omics disease signature.** TBM-specific transcriptomic/proteomic/metabolomic diagnostic biomarkers are not yet validated for routine use.

Proposed Follow-up Experiments / Actions

1. **Genotype-guided steroid trials** extending LAST ACT to pediatric and HIV-positive populations, testing whether the TT (hyperinflammatory) genotype specifically benefits.
2. **Host-directed therapy trials** of MMP-9 inhibitors (doxycycline) and pro-resolving mediators, using CSF MMP-9 and resolvin profiles as pharmacodynamic biomarkers.
3. **Optimized antibiotic PK/PD** — complete high-dose rifampicin + linezolid intensification trials (INTENSE-TBM, INSHORT, SURE) with CSF drug-exposure endpoints.
4. **Rapid molecular diagnostics scale-up** — deploy CSF tNGS/pyrosequencing for simultaneous detection and resistance profiling; develop a rule-out biomarker panel.
5. **CSF biomarker discovery** — multi-omic (proteomic/metabolomic/lipidomic) profiling to build a validated early-diagnosis and prognostic signature.
6. **Improved vaccines** — evaluate next-generation TB vaccines specifically for prevention of childhood meningeal/miliary disease.

Report compiled from 15 confirmed findings and 68 reviewed papers. Evidence sources span human clinical (RCTs, cohorts, meta-analyses), model-organism (zebrafish, mouse), and in-vitro studies, as annotated by PMID throughout.
