TB Meningitis

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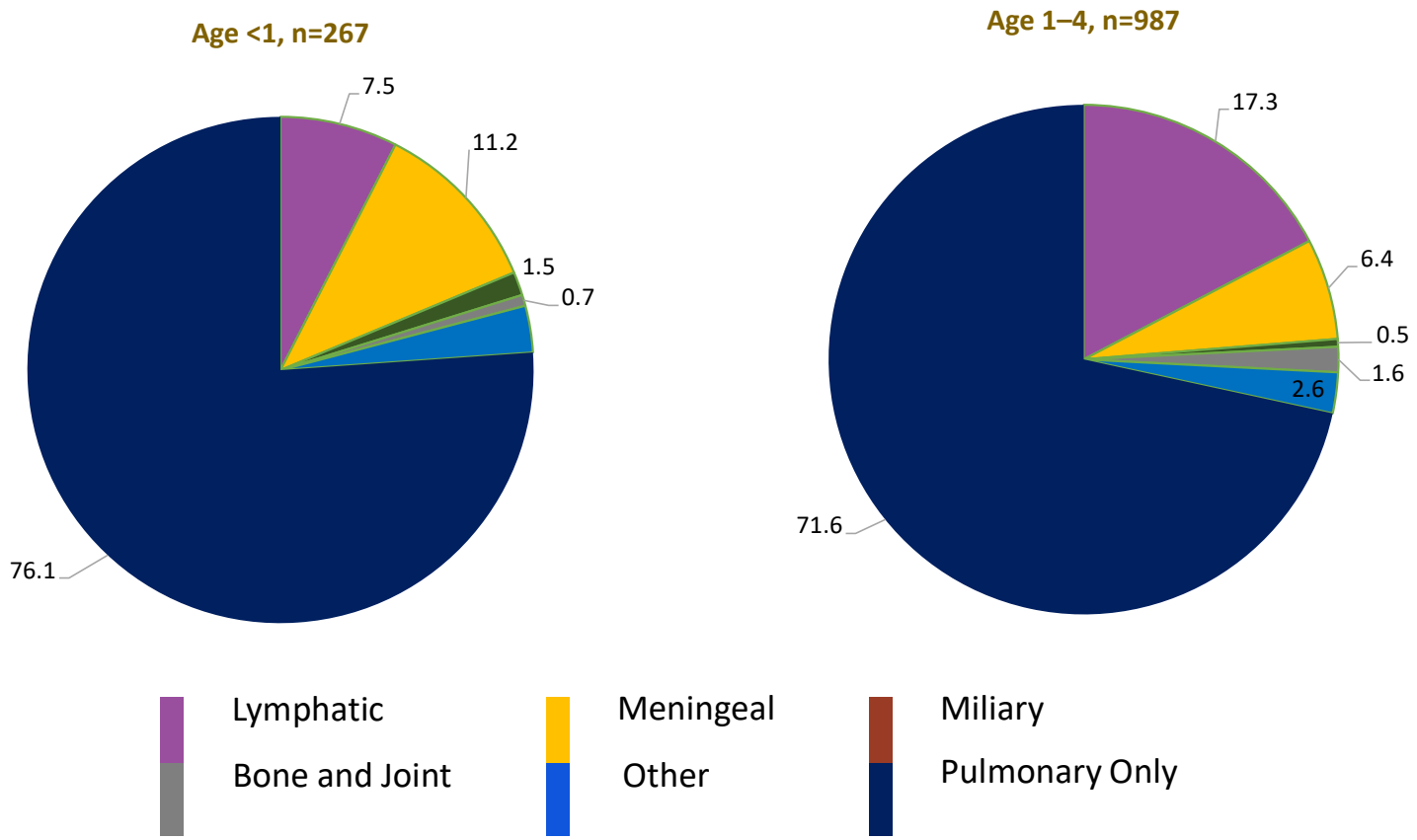
Epidemiology

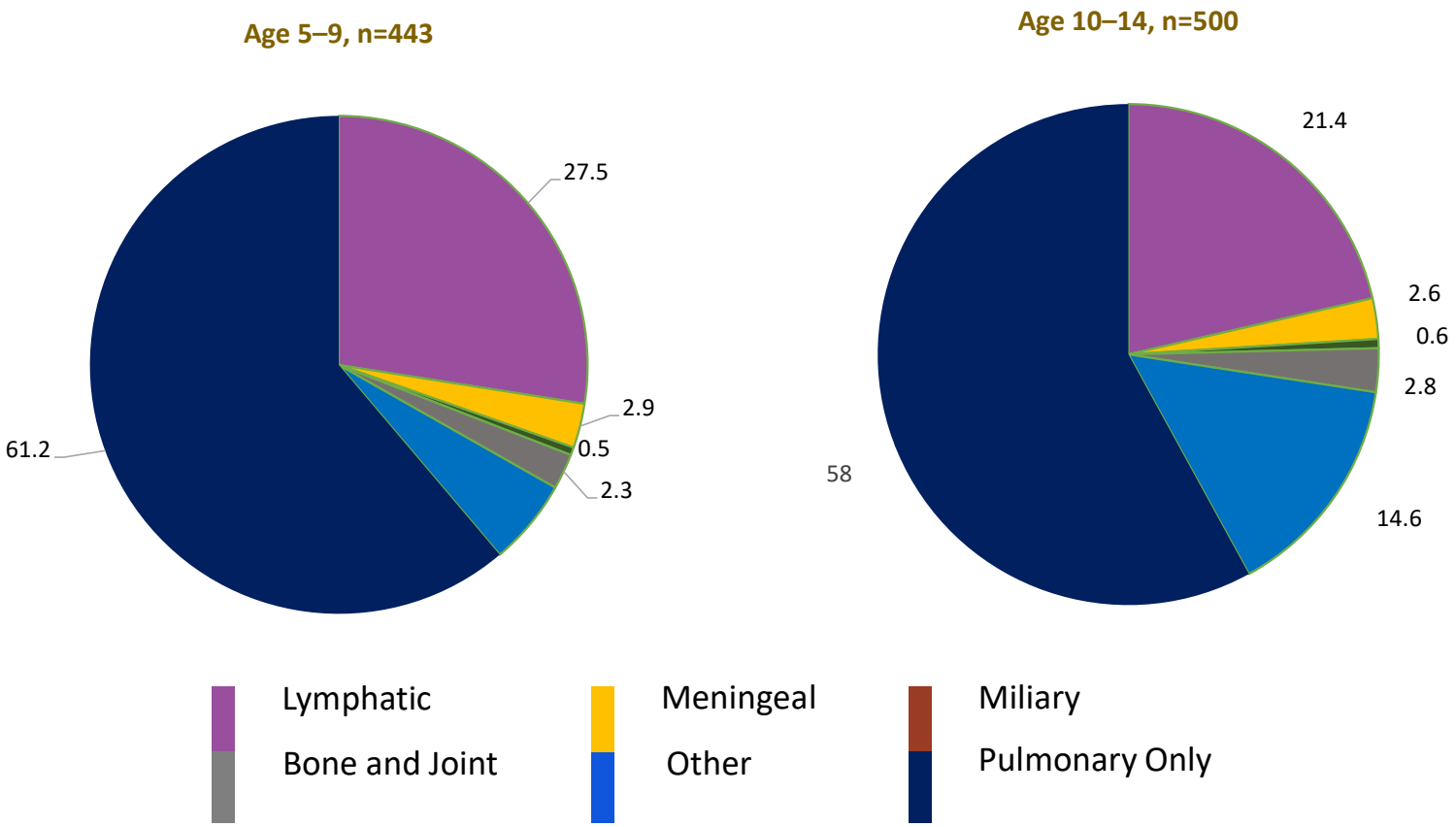
- TBM Rates are most affected by age and HIV prevalence
- 7 year population study in Germany showed **0.9%** of TB patients had TBM and children **< 5y/o had an OR 4.90**
- Brazilian study with 57, 217 cases of extrapulmonary TB showed **6%** of cases were TBM
- Extrapolation of current global data suggests there may be up to 100K cases of TBM per year
- Neonatal **BCG** is thought to be **64-73% effective in preventing TBM** (averting 30,000 cases/year)

NATURE REVIEWS | NEUROLOGY VOLUME 13 | OCTOBER 2017 | 581-598
J Neurol Neurosurg Psychiatry 2000; 68: 289-99

Percentage of TB Cases in Children with Any Extrapulmonary Involvement by Age Group (Age <5), Summed and Averaged Over 2013–2017



Percentage of TB Cases in Children with Any Extrapulmonary Involvement by Age Group (Ages 5–14), Summed and Averaged Over 2013–2017



Pathogenesis

- Rich and McCordock published an autopsy study of TBM patients
  - Observed granulomas rupturing into the subarachnoid space in nearly all the cases (Rich focus)
- Exudate at the base of the brain (basilar meningitis), histologically, includes erythrocytes, mononuclear cells, neutrophils and bacilli
- Vasculitis
  - middle cerebral arteries and Circle of Willis vessels most often affected
  - cerebral infarct found in 1/3 of patients
- TNF-α levels show some correlation with disease severity

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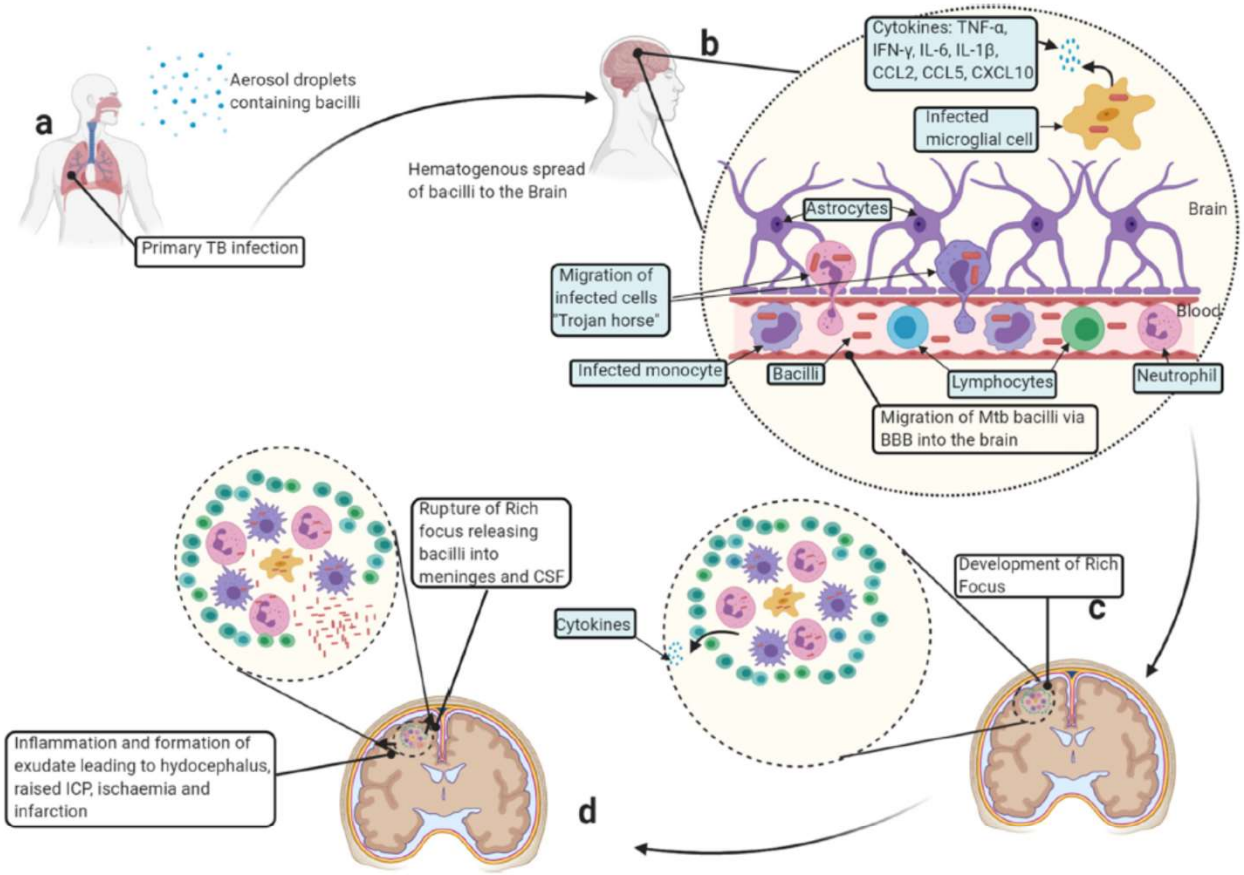

FIG 1 The generalized pathogenesis of tuberculous meningitis. (a) The host inhales aerosol droplets containing *M. tuberculosis* (Mtb) bacilli. Within the lungs, the bacilli may infect the alveolar macrophages, resulting in the formation of granuloma. The bacilli may then escape from a damaged granuloma or from the lungs during primary TB causing bacteremia, resulting in hematogenous spread of the bacteria into the brain. (b) Extracellular bacteria and infected cells may migrate through the blood-brain barrier (BBB) into the brain. Once in the brain, the bacilli infect microglial cells, which then together with infiltrating cells release cytokines and chemokines, leading to disruption of the BBB and influx of other uninfected immune cells into the brain. (c) This results in the formation of the granuloma "Rich focus." (d) When the Rich focus ruptures, the bacteria are released into the subarachnoid space, leading to dissemination of the infection to the CSF and meninges. The release of bacteria into the meninges and CSF leads to meningeal inflammation and the formation of thick exudate. The thick exudate precipitates TBM signs.

Manyelo et al. JCM. March 2021 Volume 59 (3): e01771-20

Clinical presentation

- **Stage I**
  - Notoriously nonspecific
  - Cough, low grade fever, vomiting, general listlessness
  - **Most valuable findings** are persistence of non-specific symptoms and signs, weight loss, recent contact with an active case of TB (70-80%)
- **Stage II**
  - Meningeal irritation
  - Other neurologic signs, loss of consciousness, signs of raised intracranial pressure, paralysis
- **Stage III**
  - Deep coma, progressive motor paralysis, cranial nerve palsies (especially 3rd, 6th), decerebration

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Clinical Presentation

- In children, TBM tends to develop within 3 months of infection (with 75% presenting within 12 months of infection) and the pace of infections is often rapid (weeks to months)
- Children have headache less frequently than adults
- In small children, TBM appears to be closely associated with disseminated disease
  - Recommendation to do an LP on all children < 12 months of age with active TB disease is based on this association
- Clinical presentation at diagnosis is the strongest predictor of outcome
- Hyponatremia is common (SIADH or cerebral salt wasting)

Clinical Microbiologic Reviews, Apr. 2008 p. 243-61
J Neurol Neurosurg Psychiatry 2000; 68: 289-99

Diagnosis

- AFB stain:
  - Sensitivity 10-20%
  - Large volume (10 ml), centrifuged, 30 minute examination by an experienced microscopist can increase detection to >80%
- Culture
  - More sensitive, not timely enough to effect decision making
- Xpert
  - Meta-analysis of 30 studies, found to be about 81-85% sensitive (enhanced by large volume tap, centrifugation)
- 22% TST/IGRA negative at diagnosis

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Tropical Medicine and International Health 26 (2): 122-132

Diagnosis

- Clinical suspicion!
- Typical CSF findings
  - Lymphocytes 100-1000 cells/mm^3 (first 10 days may have PMN predominance)
  - Elevated protein, decreased glucose
- Laboratory findings (pediatric TBM-review and meta-analysis)
  - Leukocytosis: **99.9%**
  - CSF lymphocytosis: **97.9%**
  - Fever: **89.9%**
  - Hydrocephalus: **86.1%**
  - CSF AFB smear positivity: **8.9%**
  - CSF AFB culture positivity: **35.1%**

Lancet Infect Dis 2014; 14: 947–57
J Neurol Neurosurg Psychiatry 2000; 68: 289-99

Table 1. Summary of TBM CSF Diagnostic Test Performance and Limitations.

Test	Sensitivity*	Specificity*	Time to Results	Strengths	Limitations
AFB Smear	10–34%	95–100%	Hours	Rapid, cheap, widely available, specificity	Poor sensitivity in most settings
Culture	48–60%	100%	2–6 weeks	Sensitivity, excellent specificity, antimicrobial resistance testing	Slow, lab infrastructure, costly, inadequate NPV
Adenosine deaminase	89%	91%	Days	Good sensitivity, low CSF volume requirement	Cost, lab infrastructure, false positives, study heterogeneity, variable test performance
IGRA	77%	88%	Days	Sensitivity	Cost, lab infrastructure, false positives, indeterminate results, varied study designs and cut-points
Antibodies	75–91%	91–98%	Days	Sensitivity	Variable study design, lack of commercial assays, false positives, numerous different targets
IL-13, VEGF, cathelicidin LL-37[a]	52%	95%	Days	Sensitivity, low CSF volume requirement	Cost, lab infrastructure, requires validation, technical expertise
IFNg, MPO, VEGF[a]	91%	100%	Days	Sensitivity, low CSF volume requirement	Cost, lab infrastructure, requires validation, technical expertise
Traditional NAAT	68–82%	100%	Days	Sensitivity, specificity	Cost, lab infrastructure, many are 'in-house' tests, variable study design, variable targets, stringent operational conditions, technical expertise
Xpert MTB/ Rif	40–70%	98–100%	Hours	Sensitivity, specificity, rapid, ease of use, detects rifampin resistance, widely distributed platform	Cost, inadequate NPV, variable study design and performance
Xpert Ultra	47–95%	100%	Hours	Sensitivity, specificity, rapid, ease of use, detects rifampin resistance, widely distributed platform	Cost, inadequate NPV, variable study design and performance
CRISPR-MTB	73%	98%	Hours	Low CSF volume, sensitivity, specificity, isothermal	Cost, lab infrastructure, stringent operational use, technical expertise, requires validation
mNGS	67%	98–100%	Days-Weeks	Can detect alternative pathogens, sensitivity, specificity	Cost, lab infrastructure, very stringent operational use, technical expertise, requires validation
Alere TB LAM	22–24%	95%	Minutes	Rapid, cost, heat stability, limited lab expertise or infrastructure requirements	Sensitivity, intra-operative variability, inadequate NPV
Fujifilm SILVAMP TB LAM	52–74%	98%	1 hour	Rapid, sensitivity, heat stability, limited lab expertise or infrastructure requirements	Cost, intra-operative variability, inadequate NPV

Cresswell. Wellcome Open Research 2021, 4:164

Radiographic Findings

- CT or MRI with contrast:
  - basal meningeal enhancement
  - Hydrocephalus (87% in children, 12% in adults)
  - infarction (28% of patients, 83% MCA distribution)
  - Tuberculomas (contrast will highlight ring-enhancement)

- Findings may worsen initially (immune mediated), has responded to corticosteroids and thalidomide

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Neuroimaging

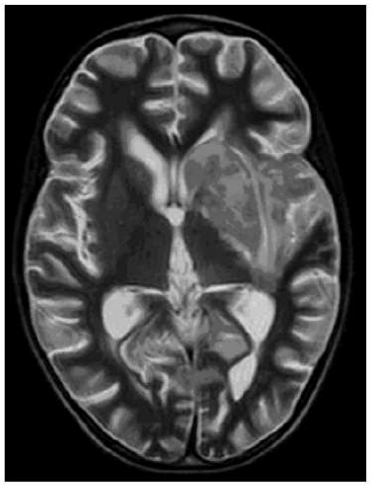


Fig. 117.1. MRI: cerebral infarction. Axial T2-weight image: heterogeneous T2 hyperintense signal change in the l middle cerebral artery distribution involving almost the enti basal ganglia, in keeping with ischemia.

Handbook of Clinical Neurology, Vol. 112 (3rd series)
Pediatric Neurology Part II, Chapter 117

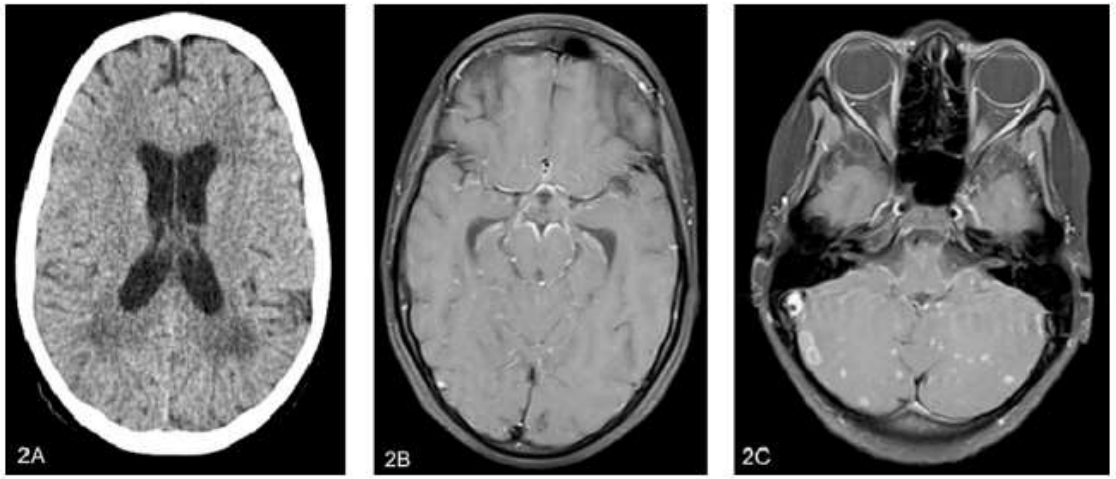
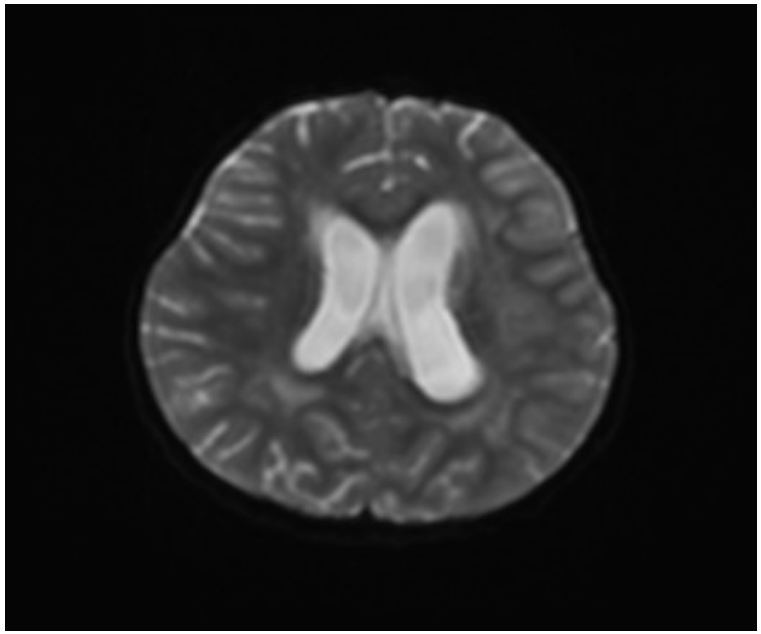
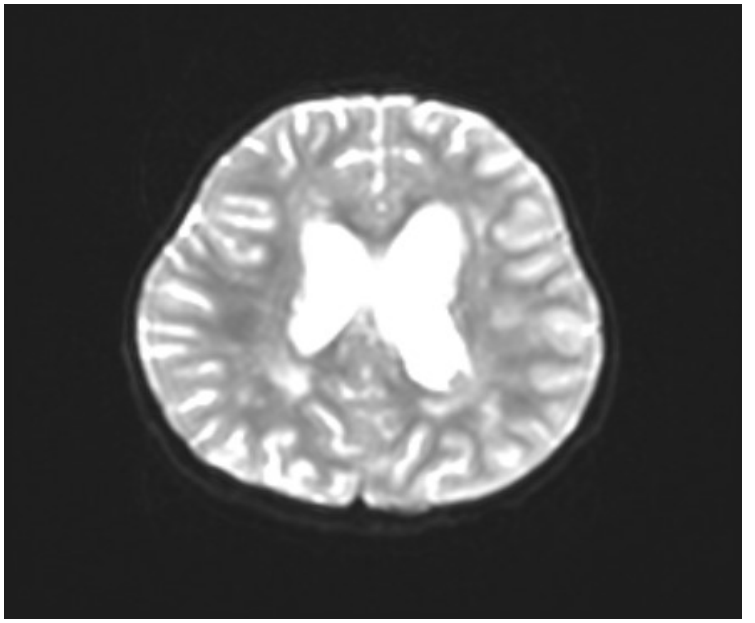


Figure 2 (A) Computed tomography scan of a 13-year-old child presenting with disseminated TB and loss of consciousness. The initial CT image only revealed bilateral periventricular hypodensities and hydrocephalus. (B and C) T1-weighted postgadolinium MR image obtained 2 days later revealed basal meningeal enhancement and multiple ring enhancing lesions (miliary nodules) in the cerebellar hemispheres. MR, magnetic resonance.

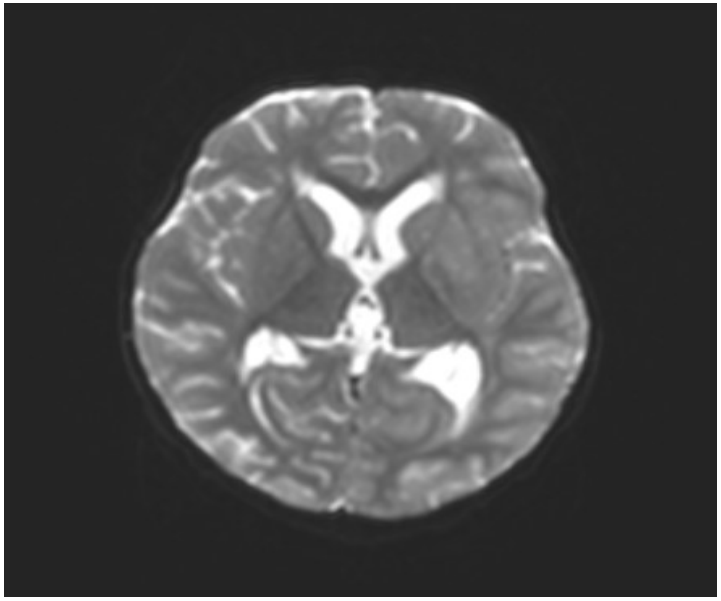
Semin Pediatr Neurol 21:12-18

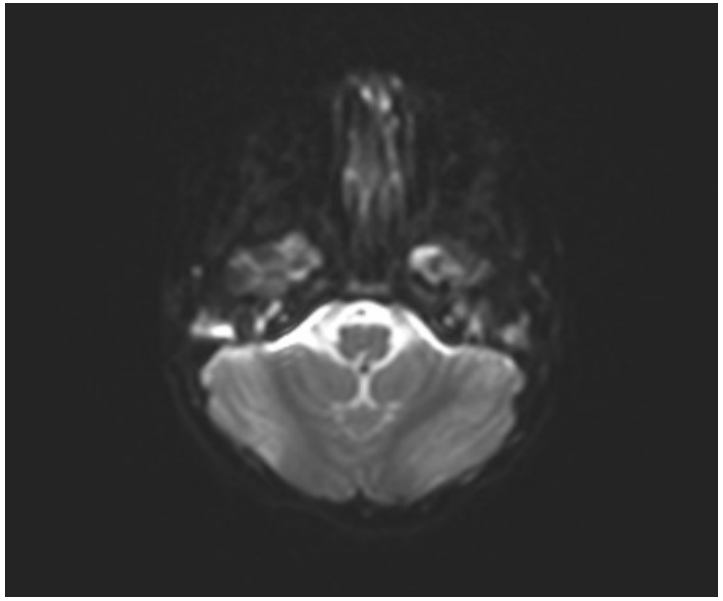
MRI with/without contrast



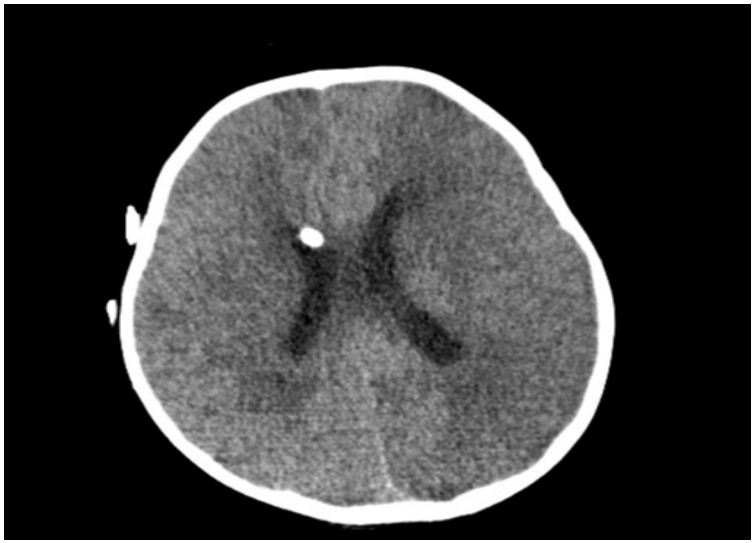


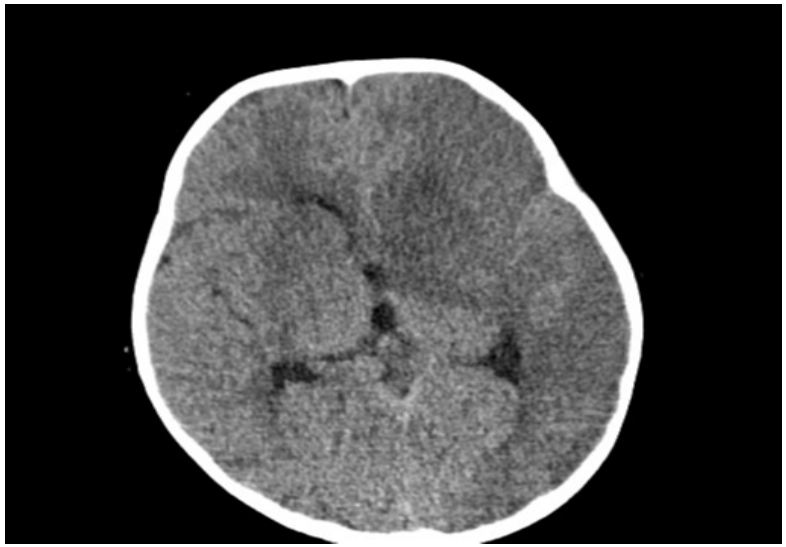
MRI with/without contrast



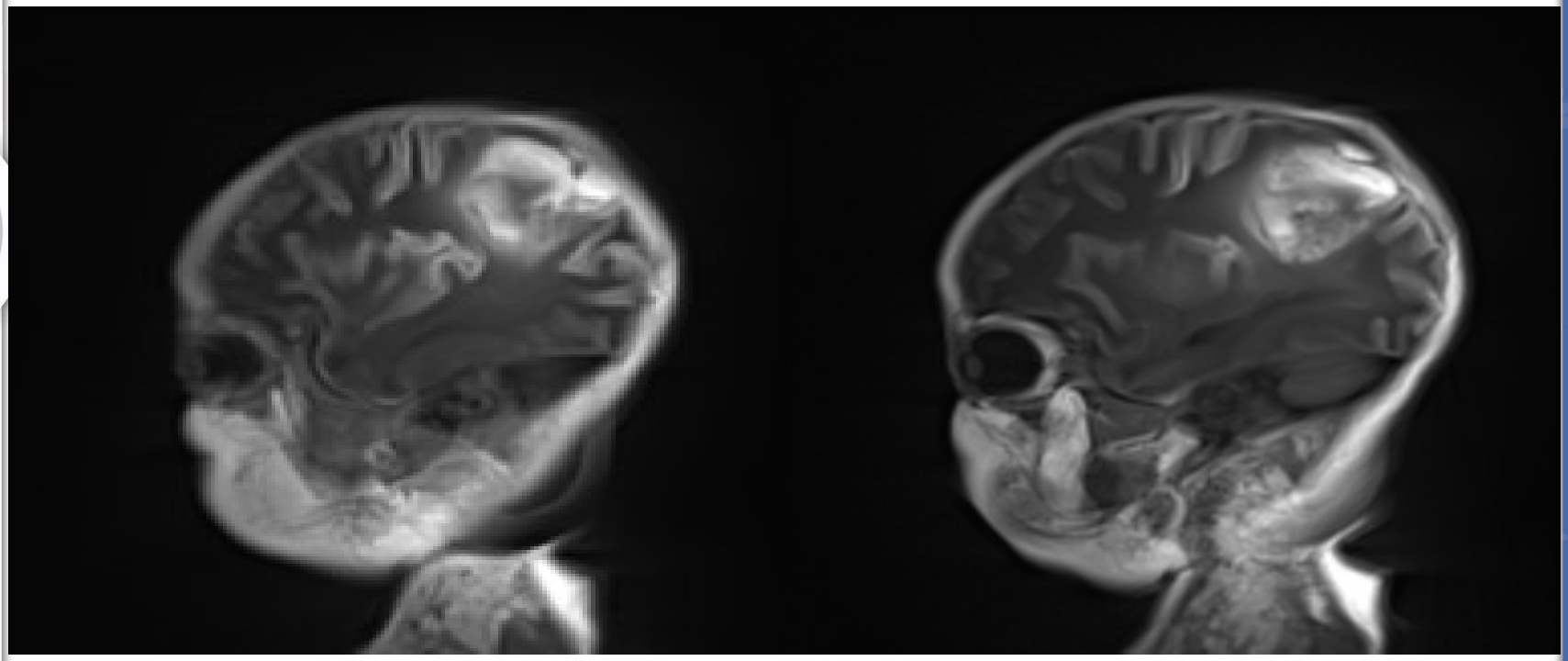


CT head Hospital day #2





Congenital TB MRI dol #30



Treatment

Treatment

- WHO: 2 months of RIPE, 10 months of INH/rifampin
  - Rifampin 20 mg/kg
- AAP Redbook: 2 months of RIP, aminoglycoside or ethionamide
  - Rifampin 20-30 mg/kg
- In South Africa, children are mostly treated for 6 months with high-dose INH, high-dose rifampin, standard dose PZA and ethionamide (in place of EMB), all 4 drugs for the entire course of treatment

Cerebrospinal Fluid Isoniazid Concentrations in Children With Tuberculous Meningitis: The Influence of Dosage and Acetylation Status

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William L. Gent, PhD‡; Heiner I. Seifart, BSc(Pharm),
Dr rea nat(Tuebingen)‡; Johan H. Lamprecht, HonBsc(Pharm), MBChB‡;
and Donald P. Parkin, BSc(Hons), MBChB‡

TABLE 1. Cerebrospinal Fluid (CSF) and Plasma Concentrations of Isoniazid as a Function of Time After Dosing at 20 mg/kg Body Weight for 27 Patients

Time, h	No. of Evaluations	CSF Concentration ± SD, μg/mL	Plasma concentration ± SD, μg/mL
0–1	1	0.9	30.6
1–2	6	8.9 ± 2.7	19.1 ± 4.2
2–3	12	11.7 ± 3.1	14.3 ± 4.2
3–4	26	12.0 ± 2.3	10.5 ± 3.0
4–5	17	10.0 ± 3.5	6.4 ± 4.1
5–6	6	5.5 ± 4.7	4.6 ± 3.5
12–14	5	1.7 ± 0.6	0.4 ± 0.4

TABLE 2. Influence of Dosage on Plasma and Cerebrospinal Fluid (CSF) Concentration of Isoniazid Over Peak CSF Range at 2 to 4 Hours After Dosing

Dosage, mg/kg body wt	n	Concentration, μg/mL ± SD	
		Plasma	CSF
10	25	4.5 ± 3.3	4.6 ± 2.4
20	40	11.2 ± 4.0	11.6 ± 2.7
C (20 mg/kg) / C (10 mg/kg)		2.5	2.5

Pediatrics 1992;89;247

Concentration of Ethambutol in Cerebrospinal Fluid in Man as a Function of the Non-Protein-Bound Drug Fraction in Serum

U. Gundert-Remy, M. Klett and E. Weber

Abteilung für Klinische Pharmakologie, Medizinische Universitätsklinik, Heidelberg, Germany (FRG)

Received: March 4, 1973

Table 3. *Serum and CSF concentrations of ethambutol in patients without meningitis (nos. 1—4), and suffering from meningitis (nos. 5—13). Patients 11—13 had tuberculous meningitis*

Pat. no.	Dose (mg/kg)	Serum conc. (μg/ml)	Free drug[a] (μg/ml)	CSF conc. (μg/ml	Duration of treatment
1	20.7	1.7	1.32	0.15	one dose
2	17.8	1.7	1.32	0.4	one dose
3	16.0	1.6	1.23	0.6	one dose
4	27.0	2.9	2.50	1.9	one dose
5	17.1	1.7	1.32	0.75	one dose
6	22.1	3.2	2.81	2.0	one dose
7	16.7	3.7	3.35	2.3	one dose
8	22.0	3.3	2.92	2.45	34 days
9	26.7	1.4	1.05	0.4	one dose
10	9.1	0.88	0.60	0.2	one dose
11	20.0	1.5	1.14	0.8	8 days
12	24.6	1.2	0.87	0.3	3 days
		1.75	1.37	0.55	25 days
		2.35	1.95	1.0	39 days
13	29.8	4.2	3.90	0.5	38 days
		3.7	3.35	0.5	60 days
	21.8	2.75	2.35	0.4	105 days
		2.3	1.90	0.6	139 days

[a] The amount of free drug was calculated from the serum concentration according to the liniar equation described in the text.

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Pouplin et al. BMC Infectious Diseases (2016) 16:144
DOI 10.1186/s12879-016-1470-x

BMC Infectious Diseases

RESEARCH ARTICLE Open Access

Naïve-pooled pharmacokinetic analysis of pyrazinamide, isoniazid and rifampicin in plasma and cerebrospinal fluid of Vietnamese children with tuberculous meningitis

Thomas Pouplin[1,2*†], Nguyen Duc Bang[3,4†], Pham Van Toi[3], Pham Nguyen Phuong[3], Nguyen Huy Dung[4], Tran Ngoc Duong[4], Maxine Caws[2,3,5], Guy E. Thwaites[2,3], Joel Tarning[1,2] and Jeremy N. Day[2,3]

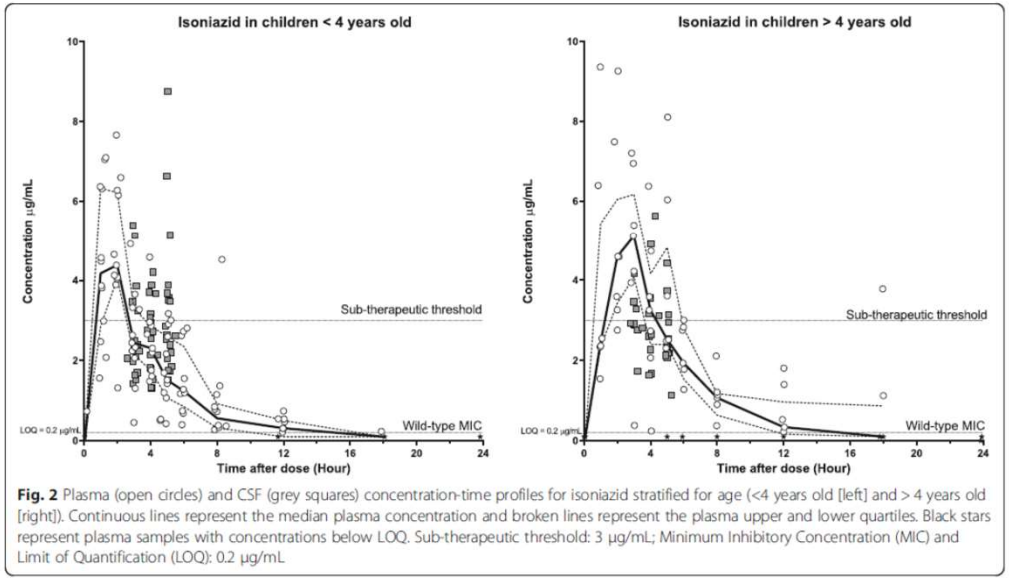

Fig. 2 Plasma (open circles) and CSF (grey squares) concentration-time profiles for isoniazid stratified for age (<4 years old [left] and > 4 years old [right]). Continuous lines represent the median plasma concentration and broken lines represent the plasma upper and lower quartiles. Black stars represent plasma samples with concentrations below LOQ. Sub-therapeutic threshold: 3 µg/mL; Minimum Inhibitory Concentration (MIC) and Limit of Quantification (LOQ): 0.2 µg/mL

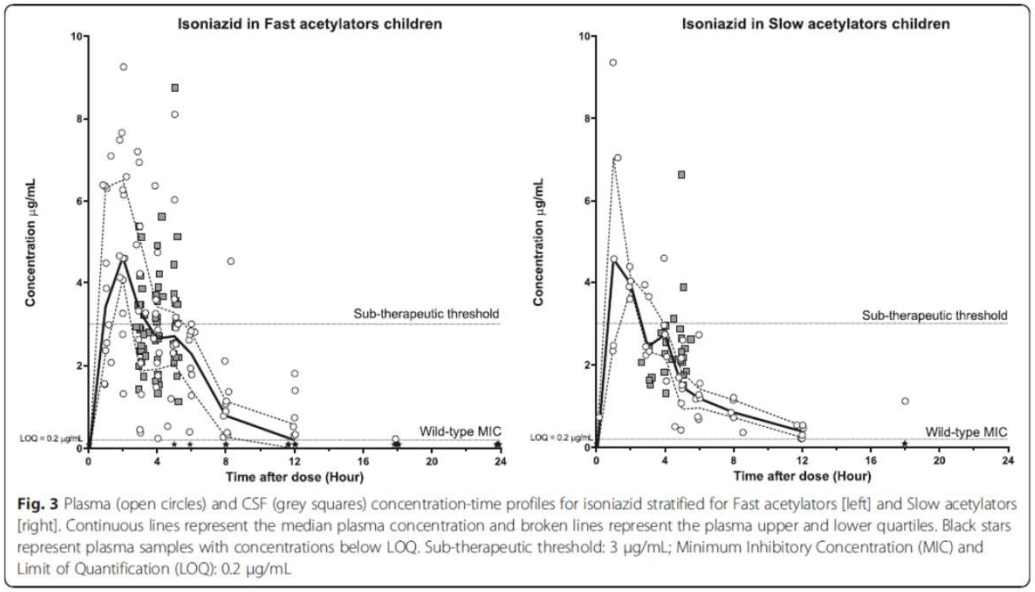

Fig. 3 Plasma (open circles) and CSF (grey squares) concentration-time profiles for isoniazid stratified for Fast acetylators [left] and Slow acetylators [right]. Continuous lines represent the median plasma concentration and broken lines represent the plasma upper and lower quartiles. Black stars represent plasma samples with concentrations below LOQ. Sub-therapeutic threshold: 3 µg/mL; Minimum Inhibitory Concentration (MIC) and Limit of Quantification (LOQ): 0.2 µg/mL

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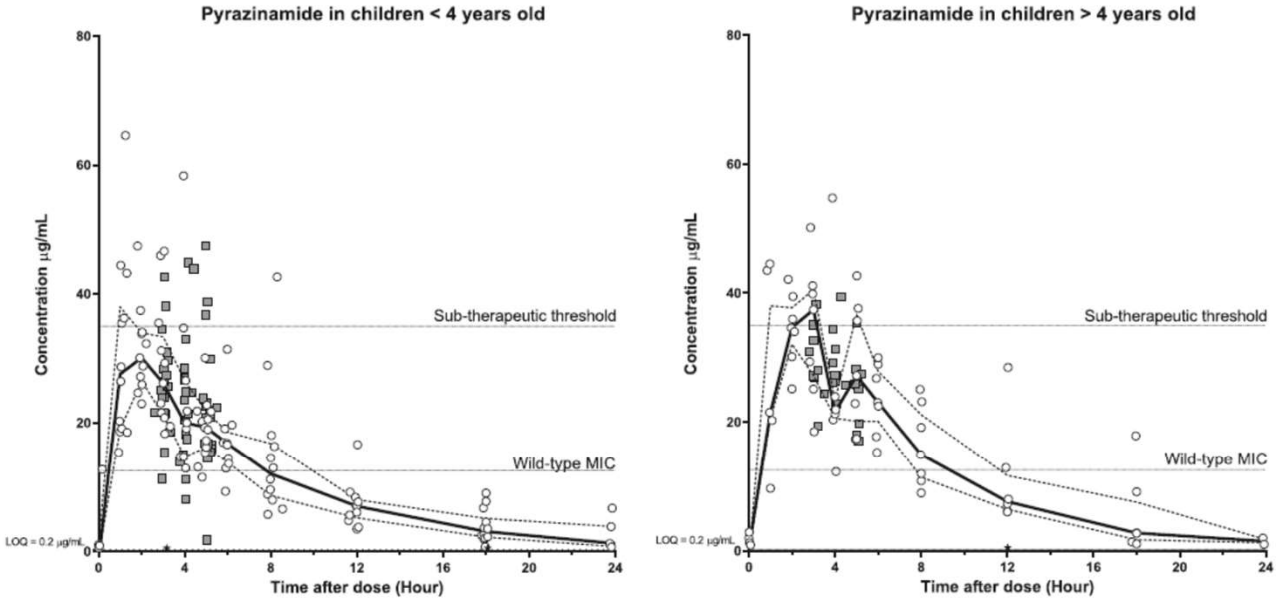

Fig. 1 Plasma (open circles) and CSF (grey squares) concentration-time profiles for pyrazinamide stratified for age (<4 years old [left] and > 4 years old [right]). Continuous lines represent the median plasma concentration and broken lines represent the plasma upper and lower quartiles. Black stars represent plasma samples with concentrations below LOQ. Sub-therapeutic threshold of 35 µg/mL; Minimum Inhibitory Concentration (MIC) of 12.5 µg/mL; and Limit of Quantification (LOQ) of 0.2 µg/mL

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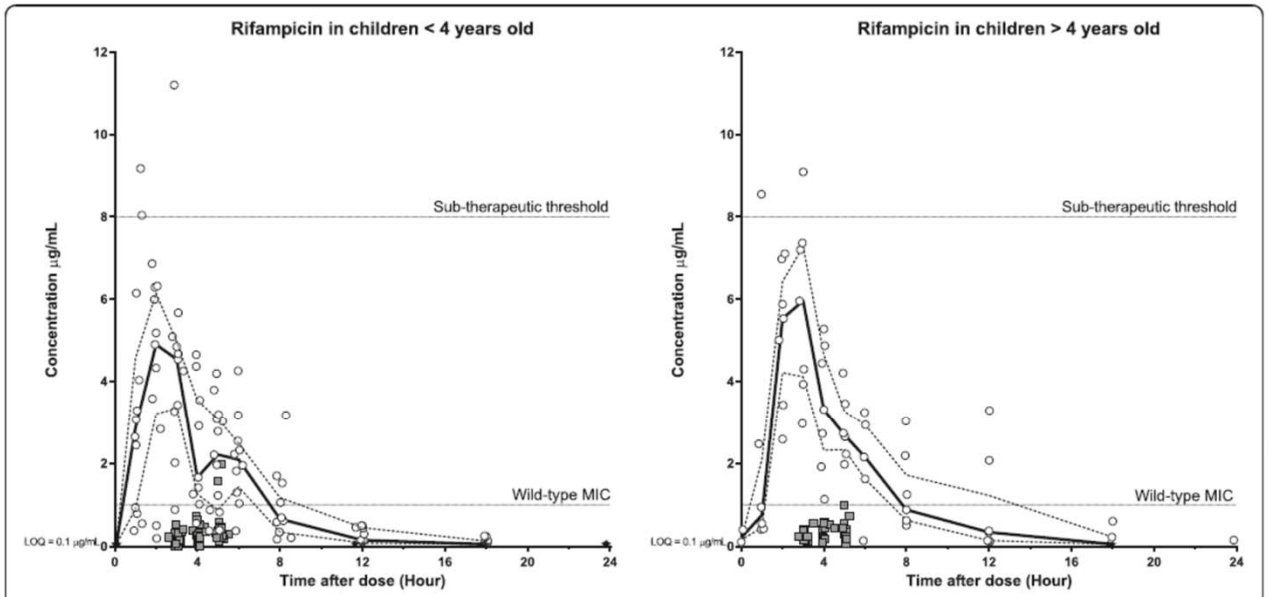

Fig. 4 Plasma (open circles) and CSF (grey squares) concentration-time profiles for rifampicin stratified for age (<4 years old [left] and > 4 years old [right]). Continuous lines represent the median plasma concentration and broken lines represent the plasma upper and lower quartiles. Black stars represent plasma samples with concentrations below LOQ. Sub-therapeutic threshold: 8 µg/mL; Minimum Inhibitory Concentration (MIC): 1.0 µg/mL; Limit of Quantification (LOQ): 0.1 µg/mL

Cerebrospinal Fluid Drug Concentrations and the Treatment of Tuberculous Meningitis

GORDON A. ELLARD, MICHAEL J. HUMPHRIES, and BRYAN W. ALLEN

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TABLE 1

CONCENTRATIONS OF ISONIAZID IN SERUM AND CSF

Hours after Dosage	Samples (*n*)	Isoniazid Dosage (*mg/kg*)	Concentration (*mg/L*)		Ratio CSF/Seru Concentration
			Serum	CSF	
2	19	8.5 ± 0.4	4.4 ± 0.5	1.9 ± 0.3	0.47 ± 0.04
4	8	9.1 ± 0.6	2.6 ± 0.8	3.2 ± 0.8	1.31 ± 0.13
5	9	9.0 ± 0.8	2.1 ± 0.6	1.8 ± 0.5	1.03 ± 0.14
6	8	7.5 ± 0.9	1.0 ± 0.3	1.8 ± 0.5	2.12 ± 0.25

TABLE 2

CONCENTRATIONS OF RIFAMPIN IN SERUM AND CSF

Hours after Dosage	Samples (*n*)	Rifampin Dosage (*mg/kg*)	Concentration (*mg/L*)		Ratio CSF/Serum Concentration
			Serum	CSF	
2	19	10.7 ± 0.5	11.5 ± 1.0	0.39 ± 0.06	0.04 ± 0.01
4	10	11.1 ± 0.5	10.6 ± 1.4	0.38 ± 0.06	0.04 ± 0.01
5	7	10.1 ± 0.6	10.1 ± 1.1	0.78 ± 0.13	0.08 ± 0.02
6	7	10.5 ± 0.8	4.7 ± 0.6	0.47 ± 0.06	0.11 ± 0.03

TABLE 4

PENETRATION OF ANTITUBERCULOSIS DRUGS INTO THE CSF, THEIR PARTITION COEFFICIENTS, PLASMA PROTEIN BINDING, RENAL EXCRETION, AND SECRETION IN THE SALIVA

Characteristic	Ethionamide	Prothionamide	Pyrazinamide	Isoniazid	Ethambutol	Streptomycin	Rifampin
Penetration into the CSF	++[26,36]*	(++)†	++[9–13]*	+‡[,8,13]*	+[8,14]*	±‡[,8,13]*	±‡[,10,13,23–25]*
Percentage ionized at body pH	0	0	0	0	> 99	> 99	> 99
Molecular weight	166	188	123	137	204	582	823
Log_{10} (partition coefficient)							
Ethyl acetate/water	1.08	1.68	−0.39	−1.17	ND§	ND	1.05
Octanol/water	1.52	2.02	−0.46	−0.84	ND	ND	1.27
Cyclohexane/water	−1.76	−1.28	−2.66	−2.54	ND	ND	−0.82
Log P_{oct}–log P_{cyh}	3.28	3.30	2.20	1.70	—	—	2.09
Plasma protein bound, (%)	30[31]*	—	0	0–4	0–25[28]*	35[21]*	85
Apparent renal clearance rate, (*ml/min*)	< 1[30]*	< 1[30]*	1–2[29]*	15[16]*‖	400–450[27,28]*¶	125	15[25]*
Predicted CSF penetration relative to pyrazinamide**	⩾ 1††	⩾ 1††	1	0.1	0.009	0.005	0.002
Secretion in the saliva			++‡	++[32]*			

Am Rev Respir Dis 1993; 148:650-5.

Drug Penetration of CSF

Table 2. Anti-tuberculosis drugs used in TBM treatment [31–34,164].

Drug	Forms	Oral bio-availability (%)	Food effect	Plasma protein binding (%)	CNS penetration (%)
First-line					
Rifampicin	PO; IV	70	–30%	89	10–20
Isoniazid	PO; IV; IM	~100	–50% C_{max}	0–10	80–90
Pyrazinamide	PO	>90	None	~10	90–100
Ethambutol	PO	75–80	None	20–30	20–30
Rifabutin	PO	50	Decreased rate of absorption	85	50
Rifapentine	PO	70	None	98	-

Expert Review of Clinical Pharmacology, 12:3, 267-288

Drug Penetration of CSF

Table 2. (Continued).

Drug	Forms	Oral bio-availability (%)	Food effect	Plasma protein binding (%)	CNS penetration (%)
Levofloxacin	PO; IV	~100	None	24–38	70–80
Moxifloxacin	PO; IV	90	None	50	70–80
Ethionamide	PO	~100	None	~30	80–90
Cycloserine	PO	65–90	Slight decrease	~0	80–90

Table 2. (Continued).

Drug	Forms	Oral bio-availability (%)	Food effect	Plasma protein binding (%)	CNS penetration (%)
Linezolid	PO; IV	~100	–23% with high-fat meals	31	70
Bedaquiline	PO	Unknown	Increase	>99	Likely poor (limited data)
Delamanid	PO	25–47	Increase	>99	No human data
Pretomanid	PO	Unknown	Increase	93	No human data

Expert Review of Clinical Pharmacology, 12:3, 267-288

Short Intensified Treatment in Children with Drug-susceptible Tuberculous Meningitis

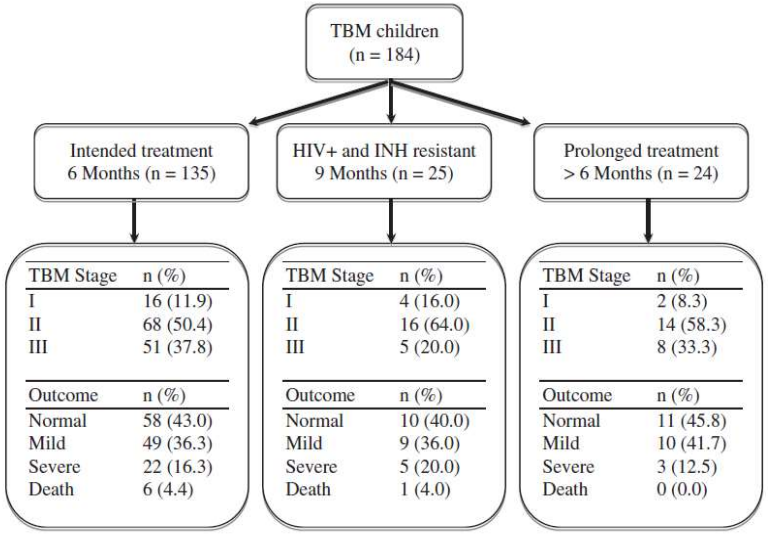
Ronald van Toorn, FCP, H. Simon Schaaf, MD,* Jacoba A. Laubscher, BCOMM,† Sabine L. van Elsland, MSc, *‡ Peter R. Donald, MD,* and Johan F. Schoeman, MD**

TABLE 3. Duration of Treatment and Reasons for Prolonged Treatment (>6 Months) in the 177 TBM Children Who Survived Completion of Therapy

Treatment Duration	HIV Negative and Not Tested (n = 156)		HIV Positive (n = 21)	
6 months	130 (83.3%)	—	6* (28.6%)	—
7 months	6 (3.9%)	6 ADIH	0 (0.0%)	—
8 months	5 (3.2%)	2 ADIH 3 poor adherence	0 (0.0%)	—
9 months	11 (7.1%)	1 INH monoresistance 1 HIV-exposed uninfected 4 TB- immune reconstitution inflammatory syndrome 5 TB mass lesions	12 (57.1%)	—
12 months	2 (1.3%)	2 TB mass lesions	2 (9.5%)	2 TB mass lesions
15 months	0 (0.0%)	—	1 (4.8%)	1 TB mass lesion
17 months	1 (0.6%)	1 INH resistance with TB mass lesion	0 (0.0%)	—
18 months	1 (0.6%)	1 TB mass lesion	0 (0.0%)	—

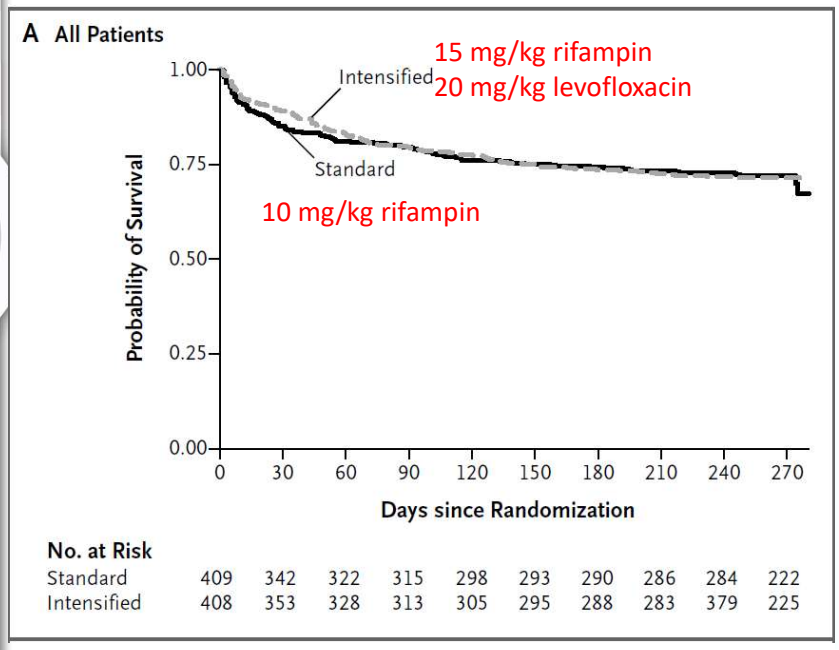
TB mass lesion refers to either large tuberculoma(s) or TB abscesses.

*All the HIV-infected TBM children who were treated for 6 months had either stage I or stage II disease.

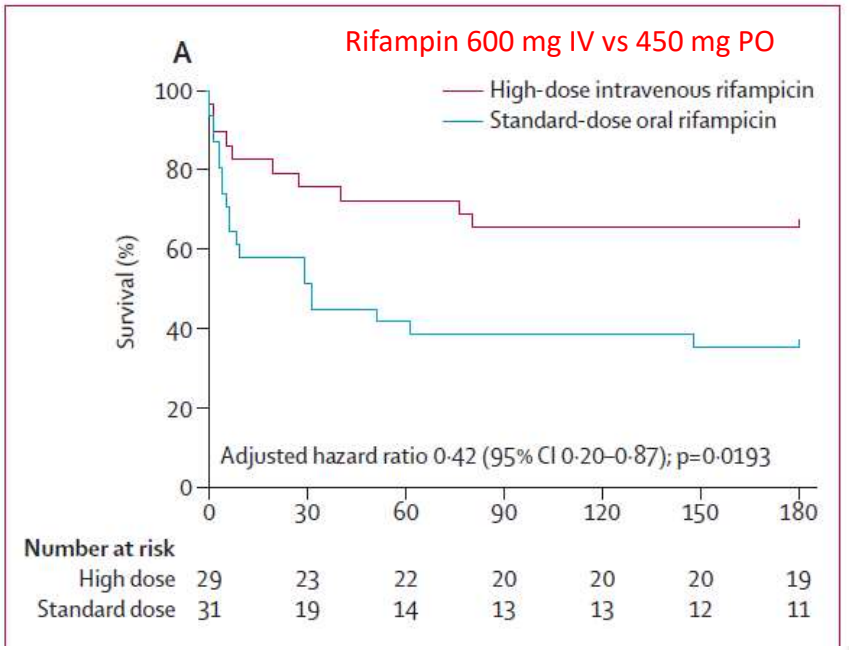


URE 1. The baseline and outcomes of TBM children who intended and received 6 months of treatment; who intended received 9 months of treatment and those who required prolonged treatment because of other reasons.

Intensified Regimen for TBM (Adults)



N Engl J Med 2016;374:124-34.



Lancet Infect Dis 2013; 13: 27–35

Linezolid is Associated with Improved Early Outcomes of Childhood Tuberculous Meningitis

Huimin Li, MD, Jie Lu, PhD,*†Jinrong Liu, MD,* Yuhong Zhao, MD,* Xin Ni, MD,*† and Shunying Zhao, MD**

TABLE 2. Characteristics of Children with Tuberculous Meningitis

Variable	LZD Group (n=36), No. (%)	Control Group (n=50), No. (%)	*P*	Total (n=86), No. (%)
Gender				
Male	21 (58.3)	30 (60.0)	—	51 (59.3)
Female	15 (41.7)	20 (40.0)	0.877	35 (40.7)
Age group (yr)				
<1	5 (13.9)	11 (22.0)	—	16 (18.6)
1–5	16 (44.4)	19 (38.0)	0.330	35 (40.7)
>5	15 (41.7)	20 (40.0)	0.431	35 (40.7)
Residence				
Rural	25 (69.4)	32 (64.0)	—	57 (66.3)
Urban	11 (30.6)	18 (36.0)	0.598	29 (33.7)
Diagnosis				
Definite	6 (16.7)	8 (16.0)	—	14 (16.3)
Probable	30 (83.3)	42 (84.0)	0.934	72 (83.7)
History of TB contact				
Yes	20 (55.6)	30 (60.0)	—	50 (58.1)
No	16 (44.4)	20 (40.0)	0.680	36 (41.9)
T-SPOT.*TB**				
Positive	33 (91.7)	45 (90.0)	—	78 (90.7)
Negative	3 (8.3)	5 (10.0)	0.793	8 (9.3)
Tuberculin skin test†				
Positive	32 (88.9.)	44 (88.0)	0.899	76 (88.0)
Negative	4 (11.1)	6 (12.0)	—	10 (12.0)
Stage				
I	2 (5.6)	4 (8.0)	—	6 (6.9)
II	17 (47.2)	27 (54.0)	1.000	44 (51.2)
III	17 (47.2)	19 (38.0)	0.849	36 (41.9)
Clinical feature				
Fever	36 (100.0)	50 (100.0)	—	86 (100.0)
Vomiting	18 (50.0)	24 (48.0)	0.915	42 (48.9)
Headache	15 (41.7)	17 (34.0)	0.625	32 (37.2)
Coma	7 (19.4)	7 (14.0)	0.568	14 (16.3)
Cranial nerve palsy	14 (38.9)	18 (36.0)	0.853	32 (37.2)
Hemiparesis	12 (33.3)	13 (26.0)	0.585	25 (29.1)

TABLE 1. Treatment Regimens for Childhood TBM Patients in This Study

Group	Regimen	Daily Dosage*
Control	2-4HRZ/10HR or 2-4HRZE/10HR	Isoniazid, 10 mg/kg/24 hr
Linezolid	2-4HRZLzd†/10HR or 2-4HRZELzd†/10HR	Rifampin, 10–15 mg/kg/24 hr Pyrazinamide, 20–30 mg/kg/24 hr Ethambutol, 15–20 mg/kg/24 hr Linezolid, 10 mg/kg/8 hr (for 0–12 years old); 600 mg/12 hr (for over 12 years old)

TABLE 3. Clinical Outcomes According to Different Treatment Regimens

Outcome and Group	Linezolid Group (n=36), No. (%)	Control Group (n=50), No. (%)	Relative Risk (95% Confidence Interval)	*P*
Outcome				
Favorable	32 (88.9)	35 (70.0)	1.00	—
Poor	4 (11.1)	15 (30.0)	3.43 (1.03–11.41)	0.037
Fever clearance time (wk)				
<1	18 (50.0)	6 (12.0)	1.00	—
1–4	12 (33.3)	18 (36.0)	4.50 (1.39–14.61)	0.010
>4	6 (16.7)	26 (52.0)	13.00 (3.61–46.82)	0.000
Duration time for hospital stays (mo)				
≤2	32 (88.9)	25 (50.0)	1.00	—
>2	4 (11.1)	25 (50.0)	8.00 (2.46–25.98)	0.000
Adverse event				
Yes	12 (33.3)	16 (32.0)	1.00	—
No	24 (66.7)	34 (68.0)	1.06 (0.43–2.65)	0.896

A Dose-Ranging Trial to Optimize the Dose of Rifampin in the Treatment of Tuberculosis

Martin J. Boeree[1,2], Andreas H. Diacon[3,4], Rodney Dawson[5,6], Kim Narunsky[5,6], Jeannine du Bois[4], Amour Venter[3], Patrick P. J. Phillips[7], Stephen H. Gillespie[8], Timothy D. McHugh[9], Michael Hoelscher[10,11], Norbert Heinrich[10,11], Sunita Rehal[7], Dick van Soolingen[12,13], Jakko van Ingen[12], Cecile Magis-Escurra[1], David Burger[14], Georgette Plemper van Balen[1], and Rob E. Aarnoutse[14]; on behalf of the PanACEA Consortium

Table 2. Possibly Related and Definitely Related Adverse Events per Grade and per Dose Group

Group	Total	Grade 1		Grade 2		Grade 3*	
		Possibly Related	Related	Possibly Related	Related	Possibly Related	Related
10 mg/kg RIF (control)	7	0	0	0	0	0	0
20 mg/kg RIF	39	21	1	4	0	2	0
25 mg/kg RIF	24	11	2	2	0	0	0
30 mg/kg RIF	39	21	3	4	0	1	0
35 mg/kg RIF	54	27	2	9	0	0	0
Total	163	80	8	19	0	3	0

Table 3. Steady-State Pharmacokinetics of Rifampin (Day 14)

Group	AUC_{0-24h} (h · mg/L)	C_{max} (mg/L)*
10 mg/kg (control)	26.3 (21.3–40.9)	7.4 (6.1–9.9)
20 mg/kg	113 (77.5–162)	21.6 (16.0–31.9)
25 mg/kg	135 (91.5–228)	25.1 (16.3–34.6)
30 mg/kg	190 (84.7–436)	33.1 (17.6–55.8)
35 mg/kg	235 (166–321)	35.2 (28.6 –44.2)

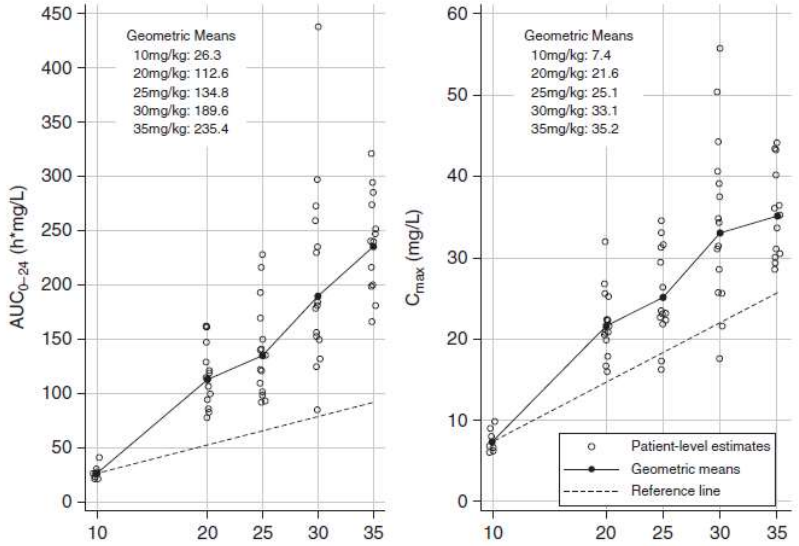


Figure 2. Distribution of exposure to rifampin (AUC, 0–24 h) at Day 14 in the various rifampin dosing groups. The *reference line* mimics a linear relationship. AUC = area under the plasma concentration–time curve; C_{max} = peak plasma concentration.

Adjunctive Therapies

- Steroids decrease mortality without affecting morbidity
- Aspirin showed clear benefit in adult patients with TBM but had no effect on morbidity or mortality in children
- Thalidamide has shown benefit

Cochrane Database of Systematic Reviews 2016, Issue 4.
J Neurol Neurosurg Psychiatry 2000; 68: 289-99
Journal of Child Neurology 26(8) 956-962

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Dexamethasone for the Treatment of Tuberculous Meningitis in Adolescents and Adults

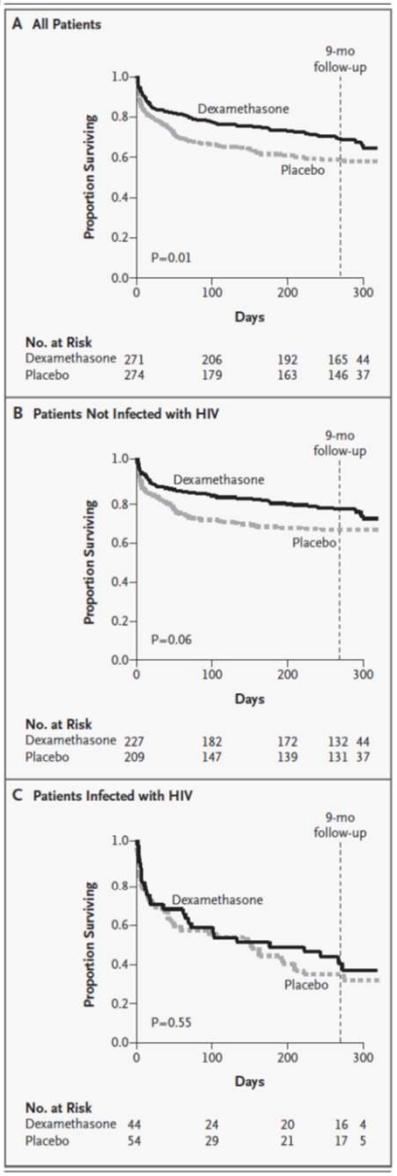
Guy E. Thwaites, M.R.C.P., Nguyen Duc Bang, M.D., Nguyen Huy Dung, M.D., Hoang Thi Quy, M.D., Do Thi Tuong Oanh, M.D., Nguyen Thi Cam Thoa, M.D., Nguyen Quang Hien, M.D., Nguyen Tri Thuc, M.D., Nguyen Ngoc Hai, M.D., Nguyen Thi Ngoc Lan, Ph.D., Nguyen Ngoc Lan, M.D., Nguyen Hong Duc, M.D., Vu Ngoc Tuan, M.D., Cao Huu Hiep, M.D., Tran Thi Hong Chau, M.D., Pham Phuong Mai, M.D., Nguyen Thi Dung, M.D., Kasia Stepniewska, Ph.D., Nicholas J. White, F.R.C.P., Tran Tinh Hien, M.D., and Jeremy J. Farrar, F.R.C.P.

N ENGL J MED 351;17 WWW.NEJM.ORG OCTOBER 21, 2004

Table 3. Outcomes of 545 Patients Nine Months after Randomization.

Group	No. of Patients	Outcome			
		Good	Inter-mediate	Severe Disability	Death
		number (percent)			
Dexamethasone*	274	104 (38.0)	49 (17.9)	34 (12.4)	87 (31.8)
Placebo	271	95 (35.1)	42 (15.5)	22 (8.1)	112 (41.3)

* Because of rounding, the percentages for the dexamethasone group do not total 100.



Thalidomide Use for Complicated Central Nervous System Tuberculosis in Children: Insights From an Observational Cohort

Ronald van Toorn,[1] Regan S. Solomons,[1] James A. Seddon,[2,3] and Johan F. Schoeman[1]

[1]Department of Paediatrics and Child Health, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa; [2]Department of Infectious Diseases, Imperial College London, London, United Kingdom; and [3]Desmond Tutu Tuberculosis Centre, Stellenbosch University, Cape Town, South Africa

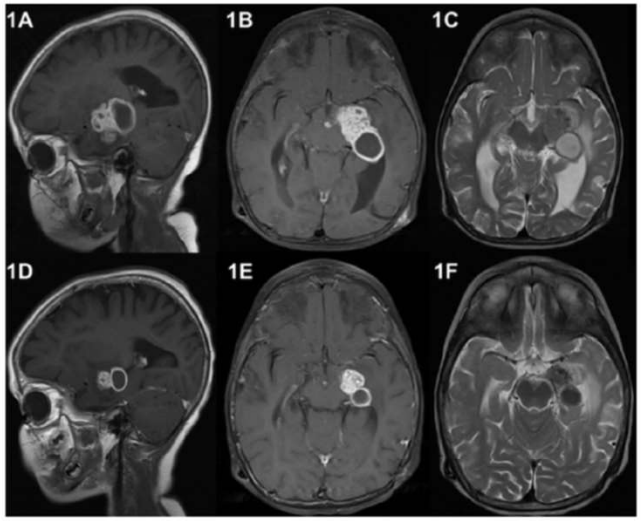


Figure 1. *A–F*, A 19-month-old human immunodeficiency virus–uninfected drug-susceptible girl who developed epilepsia partialis continua (EPC) following 2 months of anti–tuberculous meningitis therapy. *A–C*, Magnetic resonance T1 sagittal and axial postgadolinium and T2-weighted images demonstrating multiloculated TB abscesses (22 × 22 mm) in the midbrain and left temporal region. Introduction of thalidomide resulted in cessation of the EPC within 2 weeks. *D–F*, Repeat imaging after 4 months shows a reduction in the size of the abscess (12 × 15 mm) and gummatous transformation (decreased T2 signal), signifying a satisfactory treatment response.

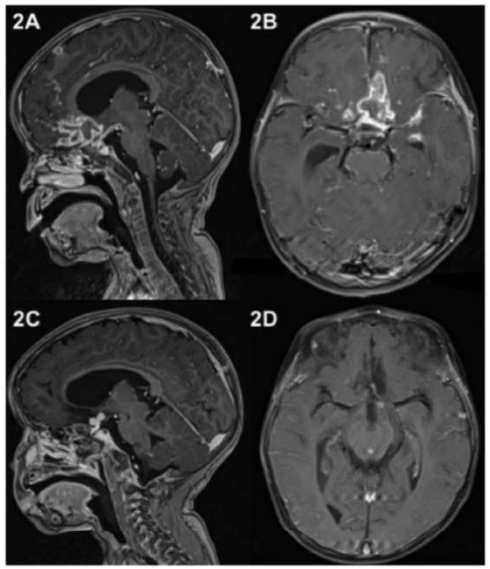


Figure 2. A 20-month-old human immunodeficiency virus–uninfected boy with tuberculous meningitis stage 2 with blindness shortly after admission. *A* and *B*, Magnetic resonance T1 sagittal and axial postgadolinium images, respectively, on admission demonstrating hydrocephalus and extensive meningeal enhancement of the basal cisterns and bilateral prechiasmatic optic nerves. Introduction of thalidomide resulted in normalization of vision within 3 weeks. *C* and *D*, Repeat imaging 4 months later showed only a single lobulated enhancing lesion (tuberculoma) and markedly decreased enhancement of the basal cisterns.

CID 2021;72(5):e136–45

Treatment Trials

Table 4
Overview of paediatric TB treatment trials*: planned or ongoing.

Study	Spectrum TB disease	Study design	Regimen	Study population and location	Primary Objectives	Status
Drug-susceptible						
OptiRif Kids Phase I	Severe (including TB meningitis) and non-severe TB	Intensive PK sampling	Escalating doses of R up to 35 mg/kg	HIV-positive infants and children 0–12 years old South Africa	Establish PK, safety and dose optimisation	Fully accrued Results expected end 2019
SHINE Phase III	Non-severe (limited) TB disease	Open label Randomised Non-inferiority	4 months (8 weeks intensive phase HRZ(E) + 8 weeks consolidation phase HR) vs 6 months (8 weeks intensive phase HRZ(E) + 16 weeks consolidation phase HR)	Children <16 years old HIV positive and negative children India, Uganda, Zambia, South Africa	Efficacy of shortened TB drug regimen given as fixed-dose combination dispersible tablets	Fully accrued Results expected 2020
TBM-KIDS Phase II	TB meningitis	Open-label Randomised	High-dose R ± Lfx, + HZ vs standard treatment HRZE	HIV-positive and negative 6 months to 12 years old India, Malawi	Efficacy, PK and safety of high-dose R to optimise TB meningitis treatment regimen	Enrolling
SURE Phase III	TB meningitis	Open-label Multifactorial Randomization Non-inferiority	Randomisation arm 1:High-dose H and High-Dose R, Lfx + pyrazinamide (6 months) vs standard TB regimen (12 months) Randomisation arm 2: Aspirin vs placebo	HIV positive and negative 28 days to 15 years old India, Zimbabwe, Zambia, Uganda, Vietnam	Efficacy and safety of shortened intensified regimen Efficacy and safety of adjuvant aspirin to improve mortality and neurodevelopmental outcomes.	Enrolment expected early 2020

Paediatric Respiratory Reviews. 2020. 36: 33-43

Outcomes

A case to consider: Initial Presentation

- 20 month old female immigrated from Afghanistan 3 days prior to presenting to an acute care clinic

- 1st visit to acute care clinic:
  - Cc/o fever, fussy for 2 days, runny nose, congestion, cough
  - Exam clear rhinorrhea, right TM dull
  - Diagnosis: AOM, given amoxicillin

- 2nd visit 6 days later:
  - Cc/o: follow up visit, subjective fevers for 2 days, n/v for 5 days (every time she eats something) vomited 3 times that day
  - Exam with exudate in both ear canals
  - Diagnosis: acute supperative OM (bilateral), rocephin IM, cefdinir, Zofran

Follow up visits

- 3rd visit 3 days later:
  - Cc/o still vomiting, 3 times that day despite Zofran, fever for 7 days, cough/congestion, no rhinorrhea
  - Exam showed exudate in bilateral ear canals, fussy throughout exam (distress over medical personnel?)
  - IM Zofran, sent to hospital for admission

- Hospital visit:
  - Admission CMP with Na+ 130, CBC with WBC 20.20, hgl 9.9/hct 32.3, plt 515.
  - Respiratory viral panel negative, abdominal US normal
  - Treated with ceftriaxone, fluids (for 'dehydration') and Zofran
  - Discharge CMP with Na+ 139

More Follow ups

- 4th clinic visit (refugee clinic) 2 days after hospital visit:
  - Still vomiting (3 times since night before), fever off and on, still taking antibiotic
  - Right ear still with discharged, left TM dull
  - HIV, Hep B core/sAg nonreactive, sAb > 1000
  - WBC 19.11, hgl 9.5/hct 31.6, plt 413
  - Na+ 131

- Three days later, the child seized and was admitted to the PICU for evaluation

Outcome

- Despite shunt placement, the patient's brain swelling worsened, testing revealed brain death
- Support was withdrawn on hospital day 5

Treatment outcomes of childhood tuberculous meningitis: a systematic review and meta-analysis

Lancet Infect Dis 2014; 14: 947–57

- 19 studies, 1636 children
- Risk of death: **19.3%**
- Probability of survival without neurologic sequelae: **36.7%**
- Risk of neurologic sequelae: **53.9%**
- Diagnosis at stage 3: **47%** (associated with worse prognosis than early diagnosis)

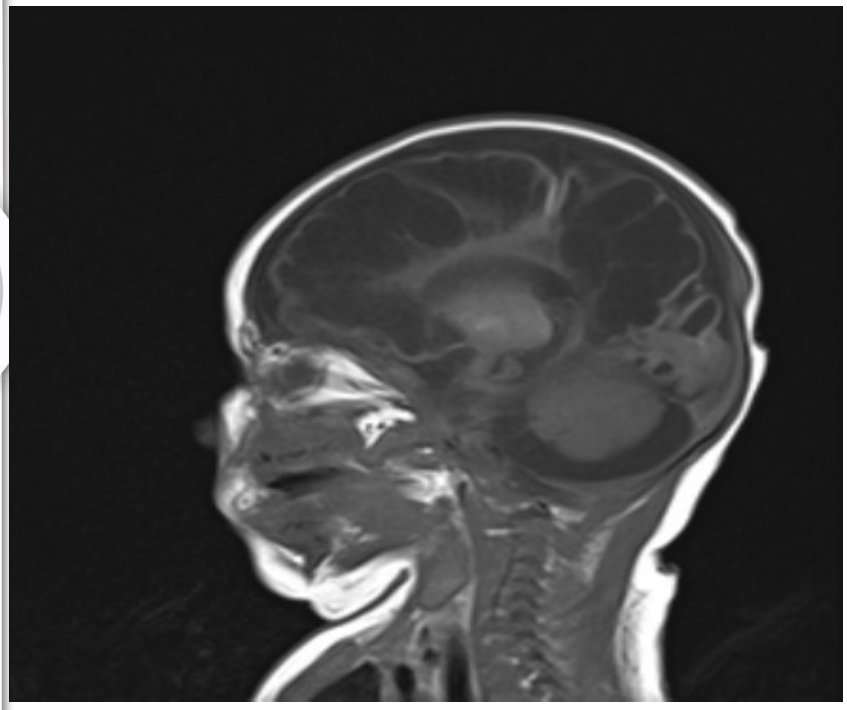
Outcomes

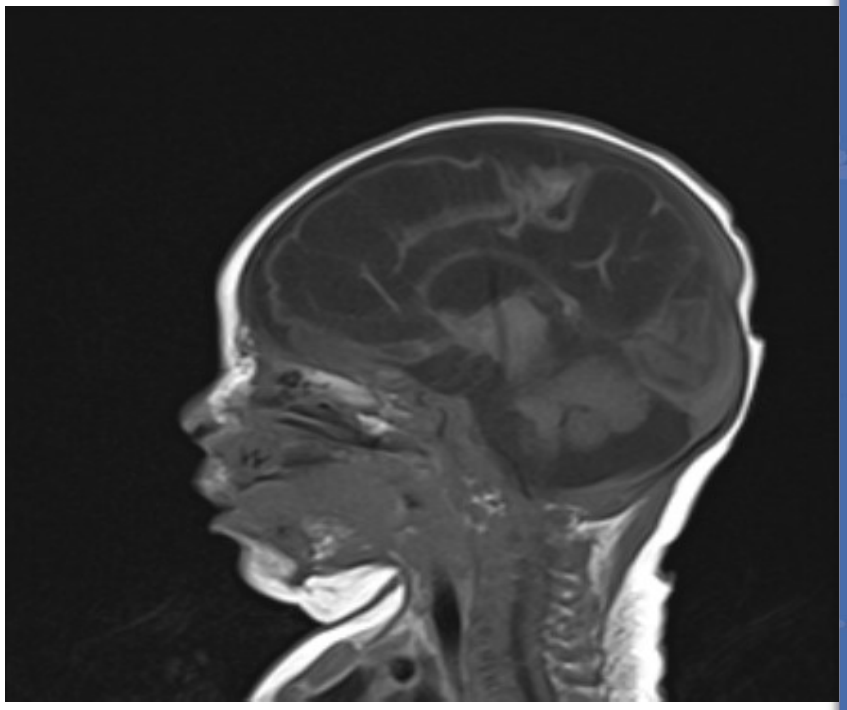
TABLE 1. British Medical Research Council clinical criteria for the severity of TBM[a]

Stage/grade	Classic criterion[b]	Contemporary criterion[c]
I	Fully conscious and no focal deficits	Alert and oriented without focal neurological deficits
II	Conscious but with inattention, confusion, lethargy, and focal neurological signs	Glasgow coma score of 14-11 or 15 with focal neurological deficits
III	Stuporous or comatose, multiple cranial nerve palsies, or complete hemiparesis or paralysis	Glasgow coma score of 10 or less, with or without focal neurological deficits

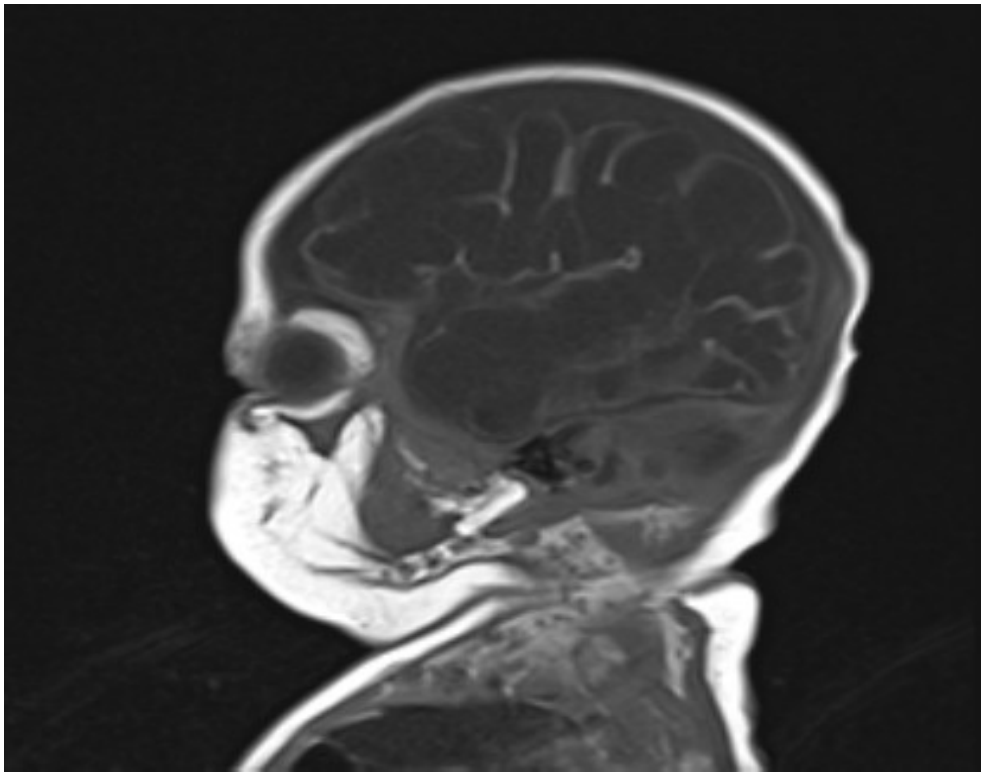
Death or Severe Disability HIV -	Death or Severe Disability HIV +
15%	25%
30%	50%
50%	80%

MRI dol #61





MRI dol #61



Some Take Home Points

- TBM is unique in children in that the brain is in the process of developing
- Early diagnosis is critical to prevent morbidity but, unfortunately, most diagnoses are made late (this needs to change)
- More studies are needed in children to maximize outcomes, from diagnosis to treatment
- Rifampin dosing….so important, so poorly done, so little data
- PK/PD data needs to be pursued (with all aggression)

Thank you for your attention

Questions?

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