International Child Health Review Collaboration

What is the most appropriate antimicrobial treatment for tuberculous meningitis?

Primary Reviewers: Julie Woodfield [1] *Secondary Reviewer*: Andrew Argent [2]

[1] *University of Edinburgh, Scotland*

[2] *University of Cape Town, South Africa*

The World Health Organization has produced guidelines for the management of common illnesses in hospitals with limited resources. This series reviews the scientific evidence behind WHO's recommendations. The WHO guidelines, and more reviews are available at: http://www.who.int/child-adolescent-health/publications/CHILD_HEALTH/PB.htm

This review addresses the question: *What is the most appropriate antimicrobial treatment for tuberculous meningitis?*

The **WHO Pocketbook of Hospital Care for Children** recommends as the optimal treatment regimen, where there is no drug resistance:

-isoniazid (10mg/kg) for 6-9 months; and

-rifampicin (15-20mg/kg) for 6-9 months; and

-pyrazinamide (35mg/kg) for the first 2 months

It does state however to follow national tuberculosis programme guidelines. (pg 151)

Introduction:

Every year, at least 1 million children develop tuberculosis (TB).[1] Clinical disease is more likely in younger, malnourished, or immuno-compromised children, which makes it a particular problem in areas with a high prevalence of HIV infection. Tuberculous meningitis (TBM) usually results from haematogenous dissemination of the tubercle bacilli, and may complicate miliary TB. The inflammatory reaction in the subarachnoid space causes arachnoid fibrosis which may lead to hydrocephalus or cranial nerve palsies, and an obliterative endarteritis can cause arterial occlusion and infarction.[2,3] Thus, while TBM is relatively rare, the consequences may be severe. Mortality remains high even with current treatment regimens, and many survivors develop serious neurological sequelae necessitating long term care. TBM therefore contributes disproportionately to the morbidity and mortality associated with *Mycobacterium tuberculosis* infection, and establishing the most appropriate antimicrobial therapy is necessary if the global burden of TB is to be addressed.

Effective antimicrobial therapy for TBM must: (1) treat the active infection by eliminating active bacilli, thus preventing neurological complications and death; (2) prevent relapse by eliminating dormant bacilli; (3) prevent the emergence of drug resistance, through combination therapy.[1] TBM treatment may also include corticosteroid therapy, and the management of complications such as hydrocephalus, raised intracranial pressure, or cerebral oedema. Until the introduction of rifampicin, standard therapy for TBM was streptomycin, isoniazid, and para-aminosalicylic acid (PAS). This combination dramatically increased survival in a previously untreatable disease.[4,5] However, with the introduction of newer antituberculous agents, mortality rates have not substantially fallen, and while all currently recommended regimens include isoniazid, rifampicin, and pyrazinamide, the inclusion of additional antimicrobials and the length of therapy are not standardised. This review aims to establish the evidence behind antimicrobial treatment recommendations, and ascertain the most appropriate antimicrobial therapy for children with TBM in hospitals with limited resources.

Methodology

Trials published in English that compared antimicrobial treatment in children with TBM were included. Case series were excluded. Articles were identified using the Pubmed Clinical Queries framework with the filters 'broad, sensitive search' and 'therapy.' The search terms were: ("Anti-Bacterial Agents"[MeSH] OR chemotherapy OR antibiotic* OR antimicrobial* OR antibacterial* OR antituberc*) AND ("Tuberculosis, Meningeal"[MeSH] OR (tubercul* AND (meningeal OR meningitis)). The Cochrane Central Register of Controlled Trials, EMBASE, SCI-Expanded, BIOSIS Previews, Global Health, African Index Medicus, Indmed, and LILACS were also searched. This identified 11 relevant articles. Four further papers were identified by hand searching reference lists of included trials. Checking references using the Web of Science cited reference tool did not identify any further papers. Of the fifteen studies identified, two could not be sourced,[6,7] four reported the same two studies,[8-11] and one, which was published as an abstract,[12] was excluded as it provided insufficient information. This left ten separate studies for analysis. Study quality was assessed using the levels of evidence of the Oxford Centre for Evidence Based Medicine. Regimens were compared for rates of death and neurological sequelae.

Results

Three randomised controlled trials were identified.[8,9,13,14] None used effective blinding, or intention to treat analysis, so all were classed as level 2b. Five non-blind non-randomised trials with historical controls were classed as level 4 poor quality cohort studies.[10,11,15-18] Two retrospective record reviews were also classed as level 4.[19,20] Levels 2b to 4 imply poor quality of investigation with a high risk of confounding, bias, or chance.

Studies were published between 1975 and 1997. All trials except one from the USA[19] took place in developing countries. The number of participants ranged from 33-199, and four included adults as well as children.[13,14,16,19] Mortality ranged from 5%-65%, with a median of 33%. Rates of sequelae, as a proportion of all patients (not survivors), ranged from 2%-58%, with a median of 32%. The majority of sequelae were pareses. Recording of sequelae and adverse effects sometimes overlapped, particularly for hearing and visual complications, which may partly explain the wide ranging values.

Two level 2b trials[8,14] and one level 4 trial[10] found no difference in mortality or sequelae with the inclusion of rifampicin in regimens, while one level 4 trial[15] found a statistically significant decrease in mortality. One level 2b[13] trial and one level 4 trial[11] comparing regimens with both rifampicin and ethambutol to those without either drug found statistically significant decreased mortality. However, while the level 2b trial[13] also found significantly less sequelae with rifampicin treatment, the level 4 trial[11] found more sequelae. Further, one level 2b trial[14] and one level 4 trial[16] found no significant difference in mortality or sequelae for regimens including ethambutol compared with those without ethambutol. One level 4 trial found a statistically significant decrease in sequelae and combined sequelae and death for a regimen containing pyrazinamide,[18] while another level 4 trial found no difference in death or sequelae with pyrazinamide treatment.[17] Both trials comparing pyrazinamide treatment used dissimilar treatment groups. Two retrospective record reviews found no association between treatment for TBM and mortality.[19,20] Papers comparing other regimens were not identified. The evidence is therefore conflicting, and of insufficient quality or quantity to establish the efficacy of rifampicin, ethambutol, or pyrazinamide treatment for TBM.

Treatment lengths varied from 6 months to 2 years, and were directly compared by two authors.[11,18] Follow up for 6 months to 8 years did not identify any relapses in any regimens, including those of 6 months duration.[11,18,20,21] No trials reported differences in mortality or sequelae with different doses of antimicrobials. Two trials reduced isoniazid[17] and rifampicin[15] doses due to a high incidence of jaundice.

Discussion

All trials assessing antimicrobial treatment for TBM had limited power, poor methodology, and varying treatment regimens with conflicting results. Therefore, it is impossible to assess the most appropriate antimicrobial regimen for TBM from the available literature.

Antimicrobial penetration of the cerebrospinal fluid (CSF) may be markedly reduced after a few months of treatment when meningeal inflammation subsides, and of the commonly used antituberculous agents, it is likely that only isoniazid,[22-24] pyrazinamide,[22,25-27] and ethionamide[28] reach their minimum inhibitory concentration in the CSF. Disseminated TB may also result in malabsorption, further reducing treatment efficacy. Streptomycin may be inadvisable in children due to otoxicity and nephrotoxicity as well as painful injections.

A recent case series reported only 26% mortality in children of advanced stage meningitis treated with 6HRZEth.[29] Therefore pyrazinamide and ethionamide could be favoured over streptomycin or ethambutol. Length of antimicrobial therapy for TBM was assessed by a recent literature review comparing case series of both adults and children. Completion and relapse rates were similar between 6 month therapy with at least HRZ and longer therapy,[30] suggesting 6 month treatment for TBM may be sufficient. However, the increasing prevalence of multidrug resistant (MDR) TB may be an important force in determining future treatment regimens.

To establish the most appropriate antimicrobial regimen for TBM in children in hospitals with limited resources, a multi-centre double-blind randomised controlled trial recruiting sufficient children to allow 80% power at the 5% significance level should be undertaken, with standard diagnostic and staging criteria applied across all centres. Six month regimens of 2HRZ/4HR, 2HRZEth/4HR, and 6HRZEth could be compared, with similar standard doses and directly observed therapy used across all treatment centres. Primary outcome measures should be death and sequelae, with follow up of at least two years after the end of therapy to assess relapses. Adverse effects should be monitored, and ideally drug resistance rates, HIV infection, and malnutrition would be recorded to allow analysis for confounding factors. In addition, the use of steroids in TBM, the use of diuretics or surgical options for managing hydrocephalus, drug interactions in TBM treatment, combined antiretroviral and TB treatment, and MDR-TB treatment for TBM all need to be investigated.

The considerable mortality and morbidity experienced by children included in this review highlights the necessity of establishing effective antimicrobial treatment for TBM if the global burden of tuberculosis is to be reduced. However, TBM needs to be managed as part of a larger tuberculosis strategy that also focuses on preventing disease through reduction of the adult reservoir of infection.

Summary

This review has found a lack of good quality evidence regarding the most appropriate antimicrobial therapy for tuberculous meningitis. Currently recommended treatment regimens have limited evidence to support them, and mortality and morbidity remain high. Further trials need to be carried out in this area.

References

1. World Health Organization. Guidance for national tuberculosis programmes on the management of tuberculosis in children. Geneva: World Health Organization; 2006. WHO/HTM/TB/2006.371.
2. Jaffe IP. Tuberculous meningitis in childhood. *Lancet* 1982; Mar 27;1(8274):738.
3. Morris JH. The Nervous System. In: Cotran RS, Kumar V, Robbins SL, editors. Robbin's Pathologic Basis of Disease. 4th ed. Philadelphia: WB Saunders; 1989. p.1385-449.
4. Streptomycin in Tuberculosis Trials Committee, Medical Research Council. Streptomycin Treatment of Tuberculous Meningitis. *The Lancet* 1948;1:582--596.
5. Lorber J. Treatment of tuberculous meningitis. *BMJ* 1960;1:1309--1312.
6. Duration of Treatment - PCMC. 1987-1996. Proceedings of the 4th Western Pacific Congress on Chemotherapy and Infectious Diseases; 1994, 4-7 December 1994; The Philippines.
7. Sunakorn P. Evolution of chemotherapy for tuberculous meningitis in childhood in Thailand. Congress of Tropical Pediatrics 1987:277--283.
8. Rahajoe NN, Rahajoe N, Boediman I, Said M, Lazuardi S. The treatment of tuberculous meningitis in children with a combination of isoniazid, rifampicin and streptomycin--preliminary report. *Tubercle* 1979; Dec;60(4):245-50.
9. Rahajoe NN, Rahajoe N, Boediman I, Said M, Lazuardi S. The treatment of tuberculous meningitis in children with a combination of isoniazid, rifampicin and streptomycin (a preliminary report). *Paediatr Indones* 1979; Nov-Dec;19(11-12):285-94.
10. Sunakorn P, Wongsaroj P. Rifampin in treatment of tuberculous meningitis in children. *J Med Assoc Thai* 1978; Feb;61(2):93-8.
11. Sunakorn P, Pongparit S, Wongrung S. Short course chemotherapy in tuberculous meningitis: a pilot trial. *J Med Assoc Thai* 1980; Jun;63(6):340-5.

12. Jacobs RF, Sunakorn P. Tuberculous Meningitis in Children: An Evaluation of Chemotherapeutic Regimens. *Am Rev Respir Dis* 1990;141:A337.
13. Chandra B. Some aspects of tuberculous meningitis in Surabaya. *Proc Aust Assoc Neurol* 1976;13:73-81.
14. Girgis NI, Yassin MW, Laughlin LW, Edman DC, Farid Z, Watten RH. Rifampicin in the treatment of tuberculous meningitis. *J Trop Med Hyg* 1978; Dec;81(12):246-7.
15. Visudhiphan P, Chiemchanya S. Evaluation of rifampicin in the treatment of tuberculous meningitis in children. *J Pediatr* 1975; Dec;87(6 Pt 1):983-6.
16. Girgis NI, Yassin MW, Sippel JE, Sorensen K, Hassan A, Miner WF, et al. The value of ethambutol in the treatment of tuberculous meningitis. *J Trop Med Hyg* 1976; Jan;79(1):14-7.
17. Ramachandran P, Duraipandian M, Nagarajan M, Prabhakar R, Ramakrishnan CV, Tripathy SP. Three chemotherapy studies of tuberculous meningitis in children. *Tubercle* 1986; Mar;67(1):17-29.
18. Jacobs RF, Sunakorn P, Chotpitayasunonah T, Pope S, Kelleher K. Intensive short course chemotherapy for tuberculous meningitis. *Pediatr Infect Dis J* 1992; Mar;11(3):194-8.
19. Porkert MT, Sotir M, Parrott-Moore P, Blumberg HM. Tuberculous meningitis at a large inner-city medical center. *Am J Med Sci* 1997; Jun;313(6):325-31.
20. Humphries MJ, Teoh R, Lau J, Gabriel M. Factors of prognostic significance in Chinese children with tuberculous meningitis. *Tubercle* 1990; Sep;71(3):161-8.
21. Ramachandran P, Duraipandian M, Reetha AM, Mahalakshmi SM, Prabhakar R. Long-term status of children treated for tuberculous meningitis in south India. *Tubercle* 1989; Dec;70(4):235-9.
22. Ellard GA, Humphries MJ, Allen BW. Cerebrospinal fluid drug concentrations and the treatment of tuberculous meningitis. *Am Rev Respir Dis* 1993; Sep;148(3):650-5.
23. Donald PR, Gent WL, Seifart HI, Lamprecht JH, Parkin DP. Cerebrospinal fluid isoniazid concentrations in children with tuberculous meningitis: the influence of dosage and acetylation status. *Pediatrics* 1992; Feb;89(2):247-50.
24. Shin SG, Roh JK, Lee NS, Shin JG, Jang IJ, Park CW, et al. Kinetics of isoniazid transfer into cerebrospinal fluid in patients with tuberculous meningitis. *J Korean Med Sci* 1990; Mar;5(1):39-45.
25. Donald PR, Seifart H. Cerebrospinal fluid pyrazinamide concentrations in children with tuberculous meningitis. *Pediatr Infect Dis J* 1988; Jul;7(7):469-71.
26. Ellard GA, Humphries MJ, Gabriel M, Teoh R. Penetration of pyrazinamide into the cerebrospinal fluid in tuberculous meningitis. *Br Med J (Clin Res Ed)* 1987; Jan 31;294(6567):284-5.
27. Phuapradit P, Supmonchai K, Kaojarern S, Mokkhavesa C. The blood/cerebrospinal fluid partitioning of pyrazinamide: a study during the course of treatment of tuberculous meningitis. *J Neurol Neurosurg Psychiatry* 1990; Jan;53(1):81-2.
28. Donald PR, Seifart HI. Cerebrospinal fluid concentrations of ethionamide in children with tuberculous meningitis. *J Pediatr* 1989; Sep;115(3):483-6.
29. Donald PR, Schoeman JF, Van Zyl LE, De Villiers JN, Pretorius M, Springer P. Intensive short course chemotherapy in the management of tuberculous meningitis. *Int J Tuberc Lung Dis* 1998; Sep;2(9):704-11.
30. van Loenhout-Rooyackers JH, Keyser A, Laheij RJ, Verbeek AL, van der Meer JW. Tuberculous meningitis: is a 6-month treatment regimen sufficient?.*Int J Tuberc Lung Dis* 2001; Nov;5(11):1028-35.

Summary Table: Rates of death and sequelae according to treatment regimen

		regimen 1				regimen 2				regimen 3				
Author Date	level of evidence[a]	regimen[b]	n	death (%)	sequelae (%)	regimen[b]	n	death (%)	sequelae (%)	regimen[b]	n	death (%)	sequelae (%)	Statistical analysis
Visudhiphan 1975	4	18HSP	13	4 (30.8)	6 (46.2)	4HR/14HP	20	1 (5.0)	7 (35.0)					none[e]
Chandra 1976	2b	?HSP	38	13 (34.2)	15 (39.5)	?HRE	42	4 (9.5)	6 (14.3)					death: $p<0.05$[f] sequelae: $p<0.01$[f]
Girgis 1976	4	2HSP/22HP	44	15 (34.1)	1 (2.3)	2HSE/22HE	42	16 (38.1)	1 (2.4)					death:ns[fg]
Girgis 1978	2b	2HSE/22HE	35	17 (48.6)	6 (17.1)	2HSR/22HR	36	18 (50.0)	6 (16.7)					none
Rahajoe 1979	2b	3HSP/9HP/6H	19	5 (26.3)	11 (57.9)	1HSR/5HR/12H	22	6 (27.3)	7 (31.8)					death: ns[f] sequelae: ns[f] $0.10>p>0.05$
Sunakorn 1980	4	2HSP/10HP	17	8 (47.1)	4 (23.5)	6HR/6HP	16	5 (31.3)	3 (18.8)	2HRSE/4HRE	16	1 (6.3)	9 (56.3)	death:ns ($p=0.3$)[fg] for 1v2 death: $p<0.05$[fg] for 1v3
Ramachandran 1986	4	2HRS/4HS$_2$E/6HE	69	18 (26.1)	28 (40.6)	2HRZS/10HE	24	8 (33.3)	9 (37.5)	2HR$_2$ZS/10HE	70	18 (25.7)	27 (38.6)	none
Humphries 1990[c]	4	P,H,S,R,E,Z,Eth	199	13 (65.3)	63 (31.7)									no associations[i]
Jacobs 1992	4	2(H/R)SE/10(H/R)E	4	2 (50.0)	2 (50.0)	2HRS/7HR	4	2 (50.0)	2 (50.0)	2HRZS/4HR	45	7 (15.6)	11 (24.4)	death: ns[fh] sequelae:$p=0.0048$[fh] death&sequelae:$p=0.0012$[fh]
Porkert 1997[c]	4	?HRZ(E/S), ?HRZ, ?HR[d]	34	17 (50.0)	6 (17.6)									no associations[i]

[a] according to the Oxford Centre for Evidence Based Medicine
[b] written in standard TB therapy code
[c] numbers for individual regimens not stated
[d] no treatment length stated
[e] no analysis performed by author but $p=0.044$ using 'Chi-square test (Table in Worksheet)' function in MiniTab
[f] X^2 test
[g] sequelae not analysed
[h] statistics are for regimen 3 v regimens 1&2 combined
[i] no statistical associations between treatment regimen and outcome

n=number of patients assigned to regimen; P=para-aminosalicylic acid; H=isoniazid; S=streptomycin; E=ethambutol; R=rifampicin; Z=pyrazinamide; Eth=ethionamide; ?=treatment duration not known; ns=not significant; none=statistics not performed