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REVIEW

The chemotherapy of tuberculous meningitis in children and adults

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SUMMARY

Literature dealing with antituberculosis chemotherapy of tuberculous meningitis (TBM) in adults and children is reviewed and recommendations made for the chemotherapy of TBM. Publications relating to the chemotherapy of TBM were reviewed which contribute to understanding the efficacy of different drugs and regimens in TBM treatment. The established classification of disease severity into stages I (no neurological signs and fully conscious), II (patients conscious but with neurological signs) and III (comatose or stuporous or with severe pareses) was used to compare regimens of isoniazid (INH), para-amino salicylic acid and streptomycin (INH regimens) used up to approximately 1970 with those using INH and rifampicin (RMP), supported by pyrazinamide and ethambutol or streptomycin (RMP regimens). Mortality in studies at all disease stages in adults or adults and children, with the children not distinguished, following INH regimens (12.4%, 25.2% and 55% at stages I, II and III respectively) did not differ significantly from that following introduction of RMP regimens (9.7%, 22.2% and 56% at stages I, II and III respectively), In studies of children only, mortality fell significantly following the introduction of RMP to 0%, 5.9% and 28.2% in children at stage I, II and III having been 10.2%, 22.3% and 49.4% respectively with INH regimens ($P = 0.006$). Following RMP regimens of 6 months duration, only 2 (1%) relapses occurred amongst 197 patients, after RMP regimens of 9–24 months only 1 (0.16%) relapse was recorded amongst 632 patients. Where INH resistance rates are <4% a directly observed INH, RMP, pyrazinamide and ethambutol for 2-months followed by INH and RMP for 4 months is recommended. If directly observed therapy cannot be practiced treatment duration should be extended to at least 9 months; if the risk of INH resistance or multidrug resistance is higher, the use of ethionamide and a fluoroquinolone and possibly cycloserine is recommended and pyrazinamide should be continued for full treatment duration. The penetration of RMP, ethambutol and streptomycin into cerebrospinal fluid is poor; higher dosages of RMP should be considered.

> "It is not unlikely that some day the absolute limits of what can be expected by tuberculocidal and tuberculostatic drugs in meningeal tuberculosis will be reached. To progress further will require additional painstaking study of the factors governing tissue response to this infection and methods of control."
> Fitzpatrick MJ 1954[1]

Introduction and methodology

Tuberculous meningitis (TBM) is arguably the most serious complication of tuberculosis and cause of death or permanent neurological damage in a significant proportion of victims. This review examines literature dealing with the antituberculosis chemotherapy of TBM in adults and children and makes recommendations for the chemotherapy of TBM. Although this review was undertaken to provide guidance for the chemotherapy of TBM in children, the literature reviewed relates to the treatment of both adults and children and the findings are likely to be equally applicable to the chemotherapy of TBM in adults.

TBM has given rise to a voluminous literature extending back more than 250 years. Medline consulted in February 2009 listed 6467 papers in response to the keywords TBM and for TBM treatment, 3178 papers; the addition of each of the major essential drugs isoniazid (INH), rifampicin (RMP) and pyrazinamide (PZA) elicited totals of 432, 192 and 99 papers respectively; TBM and streptomycin (SM) were keywords in 207 publications and cerebrospinal fluid (CSF) and INH, RMP, PZA in 148, 343 and 50 papers respectively. Confronted with this enormous literature a certain amount of subjective selection was necessary and for the purpose of this review publications appearing before February 2009 relating to the chemotherapy of TBM were selected that contribute to understanding the efficacy of different drugs and regimens in the management of TBM in children and adults. Cross referencing was an important source of further

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references particularly regarding earlier literature. Criteria used by different authors to diagnose TBM have not been questioned, unless obviously at fault. Most often cases were separated into those confirmed by *Mycobacterium tuberculosis* culture from CSF and those classified as probable TBM on the basis of *M tuberculosis* culture from another source and a constellation of clinical signs, CSF investigations, chest radiography and tuberculin testing.

Throughout the review drug dosages are given as total dosage or as mg/kg bodyweight, but without the addition of bodyweight.

The treatment of TBM has three major components: antituberculosis chemotherapy, management of raised intracranial pressure and modulation of the destructive elements of the immune response, most notably vasculitis. This review will address only one of these elements, antituberculosis chemotherapy. While antituberculosis chemotherapy of TBM is of fundamental importance to outcome, it has its best chance of success when commenced at an early stage before serious damage has occurred.

The three most important elements by which treatment response can be measured are early morbidity and mortality and relapse rates. Measurement of other, more subtle responses, such as changes in various CSF components over time, has been attempted, but has not yet thrown much light on the actions of different drugs and regimens. Access to increasingly sophisticated measurements of immune and microbiological functions may alter this position in future.[2–5]

Publications detailing the early response of TBM to treatment are numbered in hundreds. By contrast very few papers give details of relapse rates following different therapeutic regimens and the papers referenced have been carefully searched for such information. Treatment duration cannot be shortened unduly without assurance that one is not exposing patients to the danger of relapse.

The literature dealing with the pharmacokinetics of antituberculosis agents in the CSF has also been summarized, but is not dealt with in detail in this paper and is the subject of a separate paper. Almost no attempt has been made in the literature to link CSF drug concentrations to the TBM outcome, but they can be compared to what is known of the minimal inhibitory concentration (MIC) of *M. tuberculosis* for different agents and the blood concentrations of these agents associated with the successful management of pulmonary tuberculosis in clinical trials.

TBM is a disease occurring mainly in countries of the developing world and, unfortunately, the majority of cases must be managed with limited resources where study of those aspects that could contribute to a better understanding of the pathogenesis and management of TBM is limited by serious financial considerations.

The staging of severity of tuberculous meningitis

From the earliest studies of the TBM chemotherapy it was evident that prognosis was closely linked to the patient's condition at the start of treatment and this remains true. Comparison between different studies, drugs and regimens is impossible without some classification of disease severity. In one of the most often quoted papers in the field the British Medical Research Council proposed the following classification of the severity of TBM cases enrolled in their studies[6]:

Early – Patients with mainly non-specific symptoms, with little or no clinical signs of meningitis, with no pareses, in good condition, and fully conscious. Diagnosis established mainly on findings in cerebrospinal fluid (C.S.F.).
Advanced – Patients extremely ill, deeply stuporous, or comatose, or with gross pareses.
Medium – Patients in a condition between those of the first two groups.

Later practice has changed the appellation of this classification to stages I, III and II respectively. A number of variants have also been proposed and latterly the Glasgow Coma Scale has been used as an added measure of severity.[3,5,7] Throughout this review this well established classification has been used to compare results achieved in the studies reviewed; many studies used the British MRC-classification without adaptation; in some instances no clinical details were provided and these papers have not been entered into the various tables for comparison with other studies. In comparing the outcome associated with different drugs and regimens mortality has been used as being an indisputable fact. Other measures of outcome are often quantified, but their use varies considerably between different papers.

It is of historical interest to note that the Edinburgh physician Robert Whytt used much the same classification in 1768 describing the features of hydrocephalus that often accompanies TBM which he found at post mortem in a group of young children.[8]

The chemotherapy of tuberculous meningitis

In considering the most appropriate treatment for TBM it must be appreciated that there are actually very few options open to us. There are at present only five drugs recognized by World Health Organization (WHO) as 'essential' antituberculosis agents and a handful of 'second-line' or 'reserve' agents that, with the exception of the fluoroquinolones, are relatively inefficient and accompanied by a high degree of toxicity. In addition the therapeutic margin between optimal efficacy and toxicity is relatively small for most of these agents and, with the exception of most fluoroquinolones, ethionamide (ETH) and cycloserine (CS), their penetration into the CSF is poor. The development of multidrug resistance (MDR) and its appearance as a fairly frequent characteristic of *M tuberculosis* isolates from TBM patients in some regions is thus very disturbing; the exceptionally high mortality in such cases bears witness to the threat to our ability to manage TBM successfully. It is true that several new antituberculosis agents are in early clinical evaluation, but it will be some years before these drugs enter tuberculosis control programmes and even longer before we know their precise role in TBM management. It behoves us therefore to make the best possible use of existing drugs and to protect them at all costs.

The introduction of streptomycin

The chemotherapy of TBM commenced in earnest in 1946 when streptomycin (SM) became available.[9] SM was used to treat cases of TBM and miliary tuberculosis, with and without TBM, but despite the unprecedented survival of some patients, initial improvement in the patients' condition was very often followed by development of drug resistance and death. These early studies also provide an unimpeded view of the capabilities of SM in TBM treatment. An early review gave results from the USA in 100 cases of miliary tuberculosis and TBM occurring alone and together.[10] Over 18 months after commencing SM therapy of miliary tuberculosis close to 30% of patients survived; however, when complicated by TBM, or in cases of TBM alone, only approximately 10% survived. It was thus clear at this early stage that SM was far from an ideal drug to treat TBM and that its access to the central nervous system (CNS) was limited. Intrathecal SM improved these results significantly at the cost of long, complicated, painful courses of treatment, including months of intrathecal injections in many instances, but even then, only a minority of patients survived. The overall mortality associated with SM treatment in selected series ranged from 40% to 80% or 90%.[1,6,11–18] Even with

a relatively weak agent, such as SM, disease stage played a significant role in survival. In the British Medical Research Council trial 46% of patients at stage I TBM died, but 66% at stage II and 86% at stage III[6]; similar findings were reported by others.[16,19]

These early studies also demonstrated several other facts:

- The majority of deaths occurred during the first weeks after treatment start.
- Young age played a role in mortality and morbidity, although this interpretation was complicated by the fact that many younger children (<3 years of age) presented late at advanced stages of TBM.
- With experience treatment was lengthened because courses of treatment shorter than six months were frequently followed by relapse; Sir Hugh Cairns put it aptly: "we have ample evidence that treatment can be stopped to soon but none that it can be continued too long."[12] Thus despite intrathecal and IM SM *M tuberculosis* could be grown from CSF up to 11 weeks after starting treatment in some patients.
- The dosage of SM in early studies was too high and caused excessive toxicity and was reduced from 1 g daily for children of age <3 years and 2 g for those older (approximately 40 mg/kg), to dosages of approximately 20 mg/kg (maximum 1 g daily).
- The occurrence of death and disability in a minority of patients at stage I TBM at treatment commencement was noted; despite apparently optimal chemotherapy a proportion of patients deteriorated for weeks, or even months, after treatment start and this despite no evidence of microbiological failure of antituberculosis chemotherapy.

The introduction of para-amino salicylic acid

The next step forward was the introduction of para-amino salicylic acid (PAS). Although a relatively weak drug with poor CSF entry, PAS, nonetheless, assisted in protecting SM from developing resistance and an improvement in survival was immediately apparent, mortality falling by 10–20%.[1,14,17,20,21] The mean mortality in the studies referenced above where SM was used as monotherapy was 66.64%; in those studies giving treatment with PAS and SM the mortality was 47.02% ($P = 0.04$).

The isoniazid era

When INH was introduced in 1952 a major improvement in outcome of all forms of tuberculosis was immediately seen. In good hands close to 90% of TBM patients at an early disease stage managed with 'triple therapy', consisting of INH, SM and PAS, recovered fully. Pharmacokinetic studies demonstrated the excellent characteristics of INH; it was easily absorbed, spread rapidly into most tissues and body compartments including CSF and had relatively low toxicity.[1,22–25] It was also soon evident that intrathecal SM was no longer essential, although some groups continued to use this mode of SM administration for several more years and in some cases into the 1970's.[26]

A review of results during this period was presented by Fitzsimons and Smith, but cases were not differentiated as regards disease stage at treatment start.[27] Nonetheless the overall mortality was frequently less than 20%, however in a series where only stage III cases were treated survival was only 20% in the absence of intrathecal SM and 38% with its use.[28] The results of studies of TBM in adults and children using INH containing regimens are summarized in Tables 1–3, taking into account the TBM stage at treatment start. These results again show that provided the diagnosis was sufficiently early, before development of overt neurological damage, the results of treatment were nearly always good; mortality of patients at stage I disease treated with INH containing regimens was a mean of 10% and ranged from 0% to 27%. The mean mortality in all the studies listed in Table 1 (INH containing regimens with patients at stage I disease) was 11.4%, that in the studies at stage II (Table 2) 24% and amongst the patients at stage III receiving INH containing regimens (Table 3) 52.9%.

The duration of treatment during this phase of TBM treatment varied from 18 to 24 months. Treatment durations as short as six months were, however, recorded by Lorber in the United Kingdom,[30] while Kendig in the USA wrote several papers documenting successful TBM treatment with regimens six months or shorter.[48–50] Nonetheless it was generally agreed that the relapse rate was increased in regimens of less than six months and most practitioners used longer regimens.

The rifampicin and pyrazinamide era

In approximately 1970 the recently discovered agent RMP was introduced.[51] At almost the same time evidence was presented that PZA could contribute to treatment shortening.[52] Using RMP and PZA together, most patients with pulmonary tuberculosis could be treated for six months with low relapse rates during two to five year follow-up.[53] From 1970 onwards both agents were incorporated into TBM treatment regimens; when a direct comparison was made between regimens containing and not containing RMP the results were, however, disappointing; comparison of the existing "triple therapy" of INH, SM and PAS with regimens containing RMP, with or without PZA, found no significant differences, although the patient numbers enrolled were relatively small.[44,45,54,55] A single study from Indonesia enrolling 80 patients randomized to receive either "standard therapy" with INH, SM and PAS or a regimen of INH, RMP and EMB found significantly lower mortality and morbidity in the group receiving RMP.[56]The length of treatment is not stated in the paper and the results are not presented in relation to disease severity, although it is stated that the groups were initially comparable regarding the proportion of patients at stage I, II or III TBM severity. The patients were also not followed to determine relapse rates.

Tables 4–6 record the results of regimens based on INH and RMP, often accompanied by PZA and SM or EMB. In early papers recording the use of RMP in TBM emphasis was placed on the possibility that RMP might contribute to the shortening of treatment duration and several papers recorded its use in six month and nine month regimens.[60,62,65,85–87] Nonetheless, although sterilization of tuberculosis lesions and treatment shortening was one of the main advantages of the action of RMP, only a minority of papers record patient follow-up to detect relapses; most papers concentrate on documenting the short-term morbidity and mortality of TBM. Ten papers were identified that recorded observation for relapses amongst TBM patients receiving an RMP-based regimen.[45,59–63,65,72,85,88] Four of these papers enrolling 197 adults and children described the use of six month RMP containing regimens and recorded a relapse in two (1%) patients[62,65,72,85]; the remaining six papers described 632 children and adults treated for TBM with RMP containing regimens of greater than six months duration and documented only a single relapse in a treatment arm not containing RMP.[45,59–61,63,88]

The overall mortality in adults and children arising from stage I TBM cases treated with INH-based regimens (Table 1) and RMP and PZA-based regimens (Table 4) is illustrated in Figure 1A. Similarly the mortality for stages II and III TBM amongst patients

Table 1
Results of treatment of TBM stage I with INH containing regimens.

Authors	Period	Population	N	INH	SM	EMB	PAS	Corticosteroids	Duration*	Sequelae* (%)	Mortality (%)
Bulkeley[29]	1952–1953	Children	19	8 mg/kg	40 mg/kg	–	200–250 mg/kg	ACTH given to all			3 (15.8)
Lorber[30]	1952–1960	Children	55	20 mg/kg	40 mg/kg		5 g			2 (3.8%)	3 (5.5)
Pines[31]	1953–1958	Adults and children	15	10 mg/kg	Intrathecal 50–100 mg	–	300 mg/kg	Used in selected cases.	12–18 months		2 (13.3)
Voljavec & Corpe[32]	1952–1958	Children & Adults	11	8–13 mg/kg†	25–50 mg/kg†	–	200–550 mg/kg†	Patients randomized to receive cortisone	20–30 months	0	0
Arjundas & Subramaniam[33]	1957–1959	Adults (>10 years)	23	10 mg/kg	1 g		12–20 g	14 patients received corticosteroids			4 (17.4)
Lepper & Spies[18]	1947–1952	Children and adults	36	1.7 mg/kg 8 hourly	12.5 mg 12 hourly	–	60 mg/kg X 4 daily	Hydrocortisone given to 9 patients			4 (11.1)
Gosh et al[34]	1966–1969	Children <12 years	27	20 mg/kg	40 mg/kg		–	9 patients received corticosteroids			7 (25.9)
Steiner & Portugaleza[35]	1965–1973	Children 4 months–10 years	12	NP	NP		NP	–		2 (16.7%)	1 (8.3)
Sumaya et al[36]	1952–1972	Children 0–13 years	17	10–25 mg/kg	20–40 mg/kg		200–250 mg/kg	Yes		5 (29.4)	1 (5.9)
Girgis et al[37]	1970–1973	Children & adults	5	10 mg/kg	30 mg/kg, max 1 g	25/15 mg/kg‡	–	Not used	24 months		1 (20)
Girgis et al[37]	1970–1973	Children & adults	6	10 mg/kg	30 mg/kg, max 1 g		300 mg/kg	Not used	24 months		0
Idriss et al[38]	1952–1971	Children 5 months–13 years	4	20 mg/kg	20–40 mg/kg, max 1 g		200 mg/kg, max 12 g	Corticosteroids used in 84% of patients	18–24 months	0	0
Delage & Dusseault[39]	1953–1975	Children	17	NP	NP	NP	NP				4 (23.5)
Kennedy & Fallon[40]	1960–1976	9 months – 68 years	9	NP	NP	NP	NP			1 (11.1)	0
Izquierdo et al[41]	1971–1980	Children 6 months–8 years	8	10–20 mg/kg	25–30 mg/kg	20 mg/kg	200–300 mg/kg	Corticosteroids used in 50% of children	Mean duration 21 months	1 (12.5)	0
Girgis et al[42]	1979–1982	0.6–42 years	7	10 mg/kg	25 mg/kg	25/15 mg/kg§		Half of patients received dexamethasone	24 months		2 (28.6)
Girgis et al[43]	1982–1987	5 months–55 years	9	10 mg/kg	25 mg/kg, max 1 g	25/15 mg/kg§	–	Half of patients received dexamethasone	24 months		2 (22.2)

EMB = ethambutol, INH = isoniazid, NP = not provided, PAS = para-amino salicylic acid, SM = streptomycin,
* Details given when provided in relevant paper.
† Higher dosages of the drugs were used in children.
§ 25 mg/kg given for the first two months followed by 15 mg/kg.

Table 2
Results of treatment of TBM stage II with INH containing regimens.

Authors	Period	Population	N	INH	SM	EMB	PAS	Corticosteroids	Duration*	Sequelae (%) *	Mortality (%)
Bulkeley[29]	1952–1953	Children	9	8 mg/kg	40 mg/kg	–	200–250 mg/kg	ACTH given to all			0
Pines[31]	1953–1958	Adults and children	20	10 mg/kg	Intrathecal 50–100 mg	–	300 mg/kg	Corticosteroids used in selected cases.	12–18 months		3 (15)
Voljavec & Corpe[32]	1952–1958	Children & Adults	22	8–13 mg/kg†	25–50 mg/kg†	–	200–550 mg/kg†	16 patients received cortisone	20–30 months		5 (22.7)
Arjundas & Subramaniam[33]	1957–1959	Adults (>10 years)	4	10 mg/kg	1 g		12–20 g	3 patients received corticosteroids			1 (25)
Gosh et al[34]	1966–1969	Children <12 years	49	20 mg/kg	40 mg/kg		–	32 patients received corticosteroids			18 (36.7)
Steiner & Portugaleza[35]	1965–1973	Children 4 months–10 years	5	NP	NP		NP	Patients with focal neurological signs received corticosteroids		0	2 (40)
Sumaya et al[36]	1952–1972	Children 0–13 years	31	10–25 mg/kg	20–40 mg/kg		200–250 mg/kg	Yes		11 (35.5)	10 (32.3)
Girgis et al[37]	1970–1973	Children & adults	25	10 mg/kg	30 mg/kg, Max 1 g	–	300 mg/kg	Not used	24 months		7 (39)
Girgis et al[37]	1970–1973	Children & adults	22	10 mg/kg	30 mg/kg, Max 1 g	25/15 mg/kg[c]	–	Not used	24 months		7 (32)
Idriss et al[38]	1952–1971	Children 5 months–13 years	33	20 mg/kg	20–40 mg/kg, max 1 g		200 mg/kg, max 12 g	Corticosteroids used in 84% of patients	18–24 months	21 (64)	5 (15)
Delage & Dusseault[39]	1953–1975	Children	23	NP	NP	NP	NP	Used in only 6 cases with advanced disease			5 (21.7)
Kennedy & Fallon[40]	1960–1976	9 months–68 years	30	NP	NP	NP	NP	Corticosteroids used in 83% of patients		6 (20)	3 (10)
Rahajoe et al[44]	1977–1978	Children 5 months–11 years	6	20 mg/kg	30–50 mg/kg	–	200–300 mg/kg	Hydrocortisone given to all children	18 months	2 (33.3)	1 (16.7)
Izquierdo et al[41]	1971–1980	Children 6 months–8 years	22	10–20 mg/kg	25–30 mg/kg	20 mg/kg	200–300 mg/kg	Corticosteroids used in 50% of children	Mean duration 21 months	12 (54.5)	4 (18)
Girgis et al[42]	1979–1982	0.6–42 years	56	10 mg/kg	25 mg/kg	25/15 mg/kg§	–	Half of patients received dexamethasone	24 months		22 (39.3)
Doğany et al[45]	1982–1988	Adults	4	600 mg	1 g	25/15 mg/kg§	1 g	Prednisolone 1 mg/kg	12 months		1 (25)
Girgis et al[43]	1982–1987	5 months–55 years	87	10 mg/kg	25 mg/kg, max 1 g	25/15 mg/kg§	–	Half of patients received dexamethasone	24 months		28 (32.2)

EMB = ethambutol, INH = isoniazid, NP = Not provided, PAS = para-amino salicylic acid, SM = streptomycin.
* Details given when provided in relevant paper.
† Higher dosages of drugs used in children.
§ 25 mg/kg given for the first two months followed by 15 mg/kg.

Table 3
Results of treatment of TBM stage III with INH containing regimens.

Authors	Period	Population	N	INH	SM	EMB	PAS	Corticosteroids	Duration	Sequelae (%)	Mortality (%)
Bulkeley[29]	1952–1953	Children	24	8 mg/kg	40 mg/kg	–	200–250 mg/kg	ACTH given to all			8 (33.3)
Pines[31]	1953–1958	Adults and children	4	10 mg/kg	Intrathecal 50–100 mg	–	300 mg/kg	Used in selected cases.	12–18 months		2 (50)
Voljavec & Corpe[32]	1952–1958	Children & Adults	11	8–13 mg/kg*	25–50 mg/kg*	–	200–550 mg/kg*	Patients randomized to receive cortisone	20–30 months		–
Arjundas & Subramaniam[33]	1957–1959	Adults (>10 years)	24	10 mg/kg	1 g	–	12–20 g	11 patients received corticosteroids			13 (54)
Gosh et al[34]	1966–1969	Children <12 years	22	20 mg/kg	40 mg/kg	–	–	21 patients received corticosteroids			13 (59.1)
Steiner & Portugaleza[35]	1965–1973	Children 4 months–10 years	8			–	–	Patients with focal neurological signs received corticosteroids		3 (37.5)	2 (50)
Escobar et al[46]	1967–1970	Children 0–14 years	25	20 mg/kg	50 mg/kg	–	200 mg/kg	Approximately 50% of patients received corticosteroids			23 (92)
Sumaya et al[36]	1952–1972	Children 0–13 years	11	10–25 mg/kg	20–40 mg/kg	–	200–250 mg/kg	Yes		8 (72.7)	3 (27.3)
Smith[47]	1954–1969	Children 0–13 years	12	NP	NP	–	NP	Corticosteroids used in 65% of patients		6 (50)	6 (50)
Girgis et al[37]	1970–1973	Children & adults	15	10 mg/kg	30 mg/kg, Max 1 g	25/15 mg/kg†		Not used	2 years		8 (53)
Girgis et al[37]	1970–1973	Children & adults	13	10 mg/kg	30 mg/kg, Max 1 g	–	300 mg/kg	Not used	2 years		8 (62)
Idriss et al[38]	1952–1971	Children 5 months–13 years	6	20 mg/kg	20–40 mg/kg, max 1 g		200 mg/kg, max 12 g	Corticosteroids used in 84% of patients	18–24 months	2 (33)	3 (50)
Delage & Dusseault[39]	1953–1975	Children	35	NP	NP	NP	NP	Used in only 6 cases with advanced disease			18 (51.4)
Kennedy & Fallon[40]	1960–1976	9 months–68 years	2	NP	NP	NP	NP	Corticosteroids used in 83% of patients			2 (100)
Rahajoe et al[44]	1977–1978	Children 5 months–11 years	13	20 mg/kg	30–50 mg/kg	–	200–300 mg/kg	Hydrocortisone given to all children	18 months	9 (69.2)	4 (30.8)
Izquierdo et al[41]	1971–1980	Children 6 months to 8 years	4	10–20 mg/kg	25–30 mg/kg	20 mg/kg	200–300 mg/kg	Corticosteroids used in 50% of children	Mean duration 21 months	3 (75)	1 (25)
Girgis et al[42]	1979–1982	0.6–42 years	73	10 mg/kg	25 mg/kg	25/15 mg/kg[b]	–	Half of patients received dexamethasone	2 years		57 (78.1)
Doğany et al[45]	1982–1988	Adults	10	600 mg	1 g	25/15 mg/kg†	1 g	Prenisolone 1 mg/kg	12 months	4 (40)	1 (10)
Girgis et al[43]	1982–1987	5 months–55 years	182	10 mg/kg	25 mg/kg max 1 g	25/15 mg/kg†	–	Half of patients received dexamethasone	24 months		121 (66.5)

Details given when provided in relevant paper.
EMB = ethambutol, INH = isoniazid, NP = Not provided, PAS = para-amino salicylic acid, SM = streptomycin.
* Higher dosages of drugs used in children.
† 25 mg/kg given for the first two months followed by 15 mg/kg.

receiving INH-based regimens and those receiving RMP-based regimens is summarized in Tables 2 and 5 and Tables 3 and 6 respectively and the results illustrated in Figure 1B and C. In each instance the mortality following the introduction of RMP appears to be lower. Further light is shed on the mortality in Table 7 where the mortality following INH-based regimens and RMP-based regimens, summarized in Tables 1–6, is given for studies enrolling adults and children and only children. While the mortality at all disease stages following the introduction of RMP appears unchanged in studies including adults with or without children, the mortality in those enrolling only children is significantly lower, in particular for those at stage I and II TBM at the start of treatment. Unexpectedly an increase in mortality is also seen associated with year of publication. The explanation for this phenomenon is not clear, but may result from a lag period before publication and the more realistic assessment of new technology that often follows a new innovation.

Systematic literature reviews evaluating the duration of therapy for TBM have, like this review, found no studies directly comparing six month treatment regimens with nine or twelve month regimens in adults or children.[89,90] Nonetheless it was concluded by the one study that there was sufficient evidence of low relapse rates from studies recording the outcome in six month regimens and in separate studies giving the findings in longer regimens to recommend six month regimens for the treatment of TBM.[89] The authors of the second paper, writing specifically with regard to children, were of the opinion that a definitive statement could not be made and that blinded, randomized studies were required to define the best regimen for TBM treatment in children.[90]

The potential influence of pharmacokinetic and pharmacodynamic factors on the treatment of tuberculous meningitis

Several considerations have determined the constitution of regimens for pulmonary tuberculosis treatment. First and foremost is the necessity to *prevent the development of resistance*. Secondly it is desirable to *kill the great bulk of the metabolically active organisms as rapidly as possible*. Thirdly it is desirable to *kill all surviving bacilli and so prevent relapse*, and to accomplish this without undue toxicity. To achieve these aims multidrug therapy is necessary and considerable experience allows the ranking of current drugs with regard to their different capabilities.

The most effective drug for the prevention of resistance in companion drugs is INH: its action is not pH dependent, it has high early bactericidal activity (EBA), a wide therapeutic margin and an excellent tissue distribution, including very satisfactory CSF penetration in both children[91] and adults.[92] The early days of treatment of pulmonary tuberculosis are also dominated by the action of INH which is our most bactericidal drug and kills approximately 90% of the rapidly multiplying organisms present in sputum within 48 h.[93,94] This rapid action plays an important role in protecting companion drugs against the development of resistance, reduces the risk of infecting contacts and leads to a more rapid alleviation of symptoms. There is recent evidence that in TBM INH may fulfill a similar role[4]; in the presence of INH resistance CSF culture-positivity was prolonged, although the clinical outcome did not appear to be any worse in the presence of INH resistance. INH can contribute to sterilization of lesions, but probably requires at least 12 months to accomplish this. Given the excellent pharmacokinetics of INH it would seem unwise, in the absence of any other highly bactericidal drug, to omit INH from any regimen for the treatment of TBM caused by fully drug-susceptible organisms.

RMP is not as effective as INH in preventing resistance in companion drugs and allowed resistance to INH to emerge in 0.5% of patients when used in a two drug regimen.[95] Its EBA at the dosages usually used in adults (8–12 mg/kg) is approximately half that of INH,[93,96–98] but comes close to that of INH when used in higher dosages.[93,99] RMP is, however, of critical importance in sterilizing tuberculosis lesions and, together with PZA, enables current six month regimens for pulmonary tuberculosis with relapse rates of less than 5% in clinical trials. Despite these attributes there is considerable concern regarding RMP CSF concentrations; seldom are mean CSF concentrations in excess of 1 μg/ml reported at any time in patients with meningitis.[92,100–102] This can be compared to the situation in pulmonary tuberculosis where RMP concentrations in sputum of 4–12 μg/ml were found at varying times after an RMP dosage of 900 mg and 1–3 μg/ml after dosages of 600–1200 mg. In walls of tuberculosis cavities and fibrous tissue, RMP concentrations were similar to those in blood.[103] Against this background Ellard et al. considered the role of RMP in TBM to be "relatively modest".[92] It is of interest that this review found no evidence that the introduction of RMP has had a significant effect on the mortality of TBM in adults, whereas mortality in children has declined significantly. As a relatively high-dosage of RMP will often be used in children this may have contributed to the much improved outcome in children. In studies enrolling exclusively, or mainly adults, an RMP dosage of 600 mg for those weighing $\geq$50 kg and 450 mg for those $<$50 kg was often used. In studies enrolling children only, dosages varied from 10 mg/kg,[76] to 15 mg/kg,[61] 10–20 mg/kg,[67] 15–20 mg/kg,[66,74] and 20 mg/kg.[72,84] Despite doubts regarding the CSF concentrations of RMP it remains an important element in TBM treatment and appears to have been instrumental in the satisfactory outcome of TBM in patients presenting with INH-monoresistance.[4]

PZA has a very low EBA during the first 2–4 days of treatment,[93,104] although its activity over treatment days 4–14 matches that of INH and RMP. This continued bactericidal activity measured in sputum over the first 14 days of treatment means that PZA must have action against extracellular-bacilli, a point relevant to its possible action in TBM. PZA is of little value in the prevention of resistance in companion drugs, but, together with RMP, makes an essential contribution to the sterilization of lesions during six month regimens. In the context of this paper it is important to note that, even in the absence of RMP, PZA can contribute to relatively low relapse rates.[52] It should also be noted that in patients with pulmonary tuberculosis and INH resistance, PZA made a significant contribution to outcome.[53,105] Finally PZA has excellent pharmacokinetics and enters the CSF with ease reaching concentrations close to those in serum in adults and children.[106,107] In the light of concerns about the CSF concentrations of RMP and the escalating threat of INH resistance the potential role of PZA in TBM treatment should not be underestimated.

The remaining two "essential drugs" EMB and SM have limited CSF entry,[92,108,109] have low EBA and do not contribute to sterilization of pulmonary tuberculosis lesions[110] and thus probably have a limited role in TBM treatment. Increasing their dosage would probably lead to higher CSF concentrations, but at considerable risk of increased toxicity. It must, of course, be remembered that patients with TBM often also have other forms of tuberculosis where these agents will have an important role.

Finally any regimen should cause *as little toxicity as possible*. All current drugs carry some risk of toxicity and because this is often dosage dependent, toxicity is a constraining factor in any desire to raise dosages and increase efficacy. In the case of INH, RMP and PZA hepatotoxicity is the commonest problem, but careful clinical observation of patients can usually detect hepatotoxicity in time to prevent therapeutic disasters. SM and EMB ototoxicity and optic

Table 4
Results of treatment of TBM stage I with RMP containing regimens.

Authors	Period	Population	N	INH	RMP	PZA	SM	EMB	Corticosteroids	Duration	Sequelae	Mortality
Sunakorn et al[57]	1977–1979	Children	1	15 mg/kg	15 mg/kg	–	20–40 mg/kg	15 mg/kg	–	6 months	0	0
Bateman et al[58]	1970–1980	2–74 years	6	NP	NP	NP	NP	NP	Used in 84% of patients	9–24 months	1 (16.7)	0
Ramachandran et al[59]	1977–1981	Children 1–12 years	23	12 mg/kg	12 mg/kg	30 mg/kg	40 mg/kg	17.5 mg/kg	Used in all patients	12 months	3 (13%)	2 (8.7%)
Phuapradit & Vejjajiva[60]	1983–1984	Adults 17–76 years	3	300 mg	600/450 mg	1500 mg	750–1000 mg	–	Prednisolone	9 months	0	0
Visudhiphan & Chiemchanya[61]	1979–1985	Children 7 months–14 years	5	10–15 m/kg	15 mg/kg	–	–	–	Prednisolone 2 mg/kg	12 months	0	0
Alarcón et al[62]	1986–1989	11 months–70 years.	4	10 mg/kg	15 mg/kg	30 mg/kg	–	–	Prednisone 1–3 mg/kg	6 months	0	0
Humphries et al[63]	1961–1984	2 months–14 years	49	NP Used in all children	NP Used in 84% of children	NP Used in 44% of children	NP Used in 84% of children	NP Used in 47% of children	Hydrocortisone used in 73% of children	Mean 24 months	2 (4.1)	0
Waecker & Connor[64]	1976–1989	6–65 months	3	NP Used in all children	NP Used in 87% of children	NP Used in 6.7% of children	NP Used in 38% of children	NP Used in 53% of children	Steroids used in 83% of children	12 months	1 (33.3)	0
Chotmongkol[65]	1988–1990	16–61 years	7	300 mg	600/450 mg	1500 mg	750 mg	–	Prednisolone used for those depressed LOC	6 months	0	0
Altanbaşak et al[66]	1988–1992	6 months–13 years	4	15–20 mg/kg max 500 mg	15–20 mg/kg max 600 mg	–	20–40 mg/kg max 1 g	–	Dexamthasone	18–24 months	1 (25)	0
Doer et al[67]	1984–1994	3 months–15 years	6	10–15 mg/kg	10–20 mg/kg	25–35 mg/kg	20–25 mg/kg	15 mg/kg in some patients	Prednisone, prednisolone or dexamthasone	9–20 months	0	0
Doğanay et al[68]	1989–1993	Adults >15 years	7	300 mg	600 mg	1500 mg	1 g	NP	Prednisolone for all stage III cases	8–16 months		0
Verdon et al[69]	1982–1983	Mean 46 years. (18–83)	8 (20.8% HIVP)	NP	NP	NP	NP	NP	Steroids used in 64.6% 0f patients	?		0
Yechoor et al[70]	1983–1994	22–48 years	4	NP	NP	NP	NP	NP	Steroids used in 38% of patients	Median treatment duration 9 months		2 (50) (1 HIV+)
Porkert et al[71]	1984–1995	6 months–84 years	12 (8/10 HIVP)	NP	NP	NP	NP	NP	Steroids used in 47% of patients	At least 1 year		4 (33.3) (HIV?)
Donald et al[72] §	1991–1994	Median age 37 months	4	20 mg/kg	20 mg/kg	40 mg/kg	–	–	Prednisone used in 48% of patients	6 months	0	0
Hosoğlu et al[73]	1985–1996	14–67 years	16	300 mg	600 mg	1500 mg	1 g	25/15 mg/kg**	Prednisolone given to all stage III patients	At least 9 months	3 (18.8)	3 (18.8)
Yaramiş et al[74]	1988–1996	3 months–15 years.	22	10–15 mg/kg	15–20 mg/kg	25–35 mg/kg	20–25 mg/kg		Dexamethasone 0.3–0.5 mg/kg given to all patients	12 months	8 (36%)	0
Farinha et al[26]	1977–1997	8 months–16 years)	2	NP	NP	NP	NP	NP	Steroids use uncertain	12–24 months	0	0
Katrak et al[75]	1992–1997	23–57 years	3 (HIVP No ARV)	300 mg	450–600 mg	1000–1500 mg	800–1000 mg	–	Not used	uncertain	0	0
Katrak et al[75]	1992–1997	23–57 years	11 (HIVN)	300 mg	450–600 mg	1000–1500 mg	800–1000 mg	–	Not used	Uncertain	0	0
Paganini et al[76]	1989–1995	1 month–13 years	18	10 mg/kg	10 mg/kg	25–30 mg/kg		–	Steroids used in 55% of children	Mean duration 10 months	7 (38.9)	0

Lu et al[77]	1995–1999	16–83 years	13 (HIVN)	300 mg	450 mg	1500 mg	–	800 mg	Steroids used in 47% of patients	Uncertain	3 (23.1)	0
Hosoglu et al[78] *	1985–1997	18–83 years	128	300 mg	600 mg	1500 mg	1 g	25/15 mg/kg**	Steroids used in 55% of patients	At least 9 months	5 (3.6)	13 (9.4)
Thwaites et al[79]	1997–2000	Median 33 years. (90% 16–64)	8 (20% HIVP)	5 mg/kg	10 mg/kg	30 mg/kg	20 mg/kg	–	Corticosteroids not used	9 months		1 (12.5)
Wang et al[80]	1994–1999	16–80 years	19 (12.% HIVP)	NP	NP	NP	–	NP	Steroids used in 23% of patients	Median 12 months (6–18 months)	9 (47.4%)	0
Thwaites et al[3]	2001–2003	Median 35 years. (15–84)	86 (20%HIVP)	5 mg/kg	10 mg/kg	25 mg/kg	20 mg/kg	20 mg/kg	Corticosteroids not used	9 months	4 (4.7)[b]	26 (30.2)
Thwaites et al[3]	2001–2003	Median 36 years. (15–88	90 (16% HIVP)	5 mg/kg	10 mg/kg	25 mg/kg	20 mg/kg	20 mg/kg	Dexamethasone 0.4 mg/kg and tapered	9 months	4 (4.4)[b]	15 (16.7%)
Cagatay et al[81]	1991–2002	Mean 33.9 years (16–60)	17	300 mg	600 mg	2000 mg	1500 mg	–	–	12 months	0	0
Faella et al[82]	1986–2001	Median 85 months. (8–160)	5 (HIVN)	5 mg/kg	10 mg/kg	–	20 mg/kg	–	Dexamethasone 0.3 mg/kg	10–18 months	0	0

ARV = anti-retroviral drugs, EMB = ethambutol, HIVN = human immunodeficiency virus-uninfected, HIVP = human immunodeficiency virus-infected, INH = isoniazid, LOC = level of consciousness. NP = Not provided. RMP = rifampicin, SM = streptomycin.

* Treatment is not specifically stated; it is presumed to be similar to that in the author's previous paper.

† Severe disability.

§ All patients also received ETH 20 mg/kg for 6 months.

** 25/15 mg/kg given for the first two months followed by 15 mg/kg.

toxicity, respectively, are dosage related, but faced with a disease as severe as TBM, the risk can be tolerated at current dosages, even if these are not the most efficacious.

Reserve drugs that could conceivably contribute to TBM treatment by reason of efficacy or pharmacokinetic qualities include ETH and CS or one of the fluoroquinolones; of the fluoroquinolones the most attractive are ofloxacin, moxifloxacin or levofloxacin, all with good early bactericidal activity, close to that of INH[111] and relatively good entry into CSF.[112–114] ETH has good CSF penetration,[115,116] but causes hepatotoxicity and gastro-intestinal irritability, with vomiting; CS also has fairly good CSF entry, but can cause severe psychological problems.[117] PAS, even in the presence of meningitis, reaches low CSF concentrations[118] and in rabbits this is due to an active transport mechanism in the choroid plexus.[119] Nonetheless the addition of PAS to SM in early TBM regimens did improve outcome significantly.

The influence of drug resistance in tuberculous meningitis

In the absence of appropriate treatment TBM is a swift killer; in a series of children with TBM studied by Edith Lincoln, before availability of antituberculosis treatment, the mean period from diagnosis until death was 19 days[120]; there is thus no place for an attitude of 'wait and see'; the most optimal treatment must be started as soon as possible. Immediately after SM introduction, drug resistance became apparent and seriously limited the early successes of SM. The introduction of PAS and later INH addressed this problem preventing the emergence of resistant-mutants and rates of resistance were maintained at low levels for several decades; the danger of drug resistance to successful TBM treatment was, however, recognized.[17]

From approximately the late 1960's case-reports and descriptions of TBM management refer more frequently to the occurrence of drug resistance.[35,121,122] In several cases INH resistance was associated with treatment failure and death and the authors emphasize the importance of a good history to detect possible drug-resistant contacts to assist in prescribing appropriate therapy as early as possible. The importance of these cases, and later cases of MDR TBM, lies in their ability to demonstrate the relative efficacy of different drugs for TBM treatment and the effect of their absence on the remaining drugs. In the case of regimens of INH, SM and PAS, with possibly EMB added after 1970, the loss of INH often paved the way for resistance to the other drugs, and, sooner or later death.

With the availability of RMP it was hoped that the gap caused by INH resistance might be closed, however this was not always the case. Fallon describes the poor response of a TBM patient receiving INH, RMP and EMB; identification of INH resistance in an *M tuberculosis* isolate from the CSF led to the substitution of ETH for INH and a satisfactory resonse.[123] In the report of Waeker and Connor a child with TBM was treated with INH, RMP, and EMB (dosages not stated) and 2 weeks after treatment commencement remained CSF culture-positive.[64] At this point a brain biopsy, undertaken while inserting a ventriculo-peritoneal shunt, was also still culture-positive for *M tuberculosis* and the isolate was resistant to INH.

Two case-reports describe the treatment of miliary tuberculosis not initially affecting the CNS, with regimens of INH, RMP, PZA and EMB.[124,125] In both cases the chest radiograph cleared and the patients improved clinically, but despite this TBM developed, suggesting that the companion drugs were unable to prevent development of CNS tuberculosis. This course of events led the one group of authors to emphasize that the CNS should be regarded as "a unique therapeutic compartment" and that the differential penetration of drugs into the CSF and CNS is important and must be

Table 5
Results of treatment of TBM stage II with RMP containing regimens.

Authors	Period	Population	N	INH	RMP	PZA	SM	EMB	Corticosteroids	Duration	Sequelae	Mortality
Rahajoe et al[44]	1977–1978	Children 5 months–11 years	13	20 mg/kg	10–15 mg/kg	–	30–50 mg/kg	–	All children received corticosteroids	18 months	0	0
Sunakorn et al[57]	1977–1979	Children	9	15 mg/kg	15 mg/kg	–	20–40 mg/kg	15 mg/kg	–	6 months	3	1
Bateman et al[58]	1970–1980	2–74 years	22	NP	NP	NP	NP	NP	Used in 84% of patients	9–24 months	7 (31.8)	3 (13.7)
Ramachandran et al[59]	1977–1981	Children 1–12 years	125	12 mg/kg	12 mg/kg	30 mg/kg	40 mg/kg	17.5 mg/kg	Steroids used in all children	12 months	58 (46.4%)	31 (24.8%)
Phuapradit & Vejjajiva[60]	1983–1984	Adults 17–76 years	16	300 mg	600/450 mg	1500 mg	750–1000 mg	–	Prednisolone	9 months	2 (12.5)	0
Doğany et al[45]	1982–1988	Adults	6	600 mg	600 mg	–	1 g	–	Prednisolone 1 mg/kg or dexamethasone for raised intracranial pressure.	12 months	1 (16.7)	3(50)
Visudhiphan & Chiemchanya[61]	1979–1985	Children 7 months–14 years	23	10–15 m/kg	15 mg/kg	–	–	–	Prednisolone 2 mg/kg	12 months	5 (21.7)	0
Alarcón et al[62]	1986–1989	11 months–70 years. HIV not evaluated.	10	10 mg/kg	15 mg/kg	30 mg/kg	–	–	Prednisone 1–3 mg/kg	6 months	2 (20%)	0
Humphries et al[63]	1961–1984	2 months–14 years	78	NP Used in all children	NP Used in 84% of children	NP Used in 44% of children	NP Used in 84% of children	NP Used in 47% of children	Hydrocortisone used in 73% of children	Mean 24 months	16 (20.5)	1 (1.3%)
Waecker & Connor [64]	1976–1989	6–65 months	10	NP Used in all children	NP Used in 87% of children	NP Used in 6.7% of children	NP Used in 38% of children	NP Used in 53% of children	Steroids used in 83% of children	12 months	7 (70)	0
Chotmongkol[65]	1988–1990	16–61 years	12	300 mg	600/450 mg	1500 mg	750 mg	–	Prednisolone used for those depressed LOC	6 months	1 (8.3)	1 (8.3)
Altanbaşak et al[66]	1988–1992	6 months–13 years	28	15–20 mg/kg max 500 mg	15–20 mg/kg max 600 mg	–	20–40 mg/kg max 1 g	–	Dexamthasone	18–24 months	17 (60.7)	1 (3.6)
Doer et al[67]	1984–1994	3 months–15 years	13	10–15 mg/kg	10–20 mg/kg	25–35 mg/kg	20–25 mg/kg	15 mg/kg in some patients	Prednisone, prednisolone or dexamthasone	9–20 months	2 (15.4)	1 (7.7)
Doğanay et al[68]	1989–1993	Adults > 15 years	34	300 mg	600 mg	1500 mg	1 g	NP	Prednisolone for all stage III cases	8–16 months		2 (5.9%)
Moling & Mian[83]	1982–1993	24–69 years	8	NP	NP	NP			–	Not stated		4 (50%)
Verdon et al[69]	1982–1983	18–83 years	11 (20.8% HIVP)	NP	NP	NP	NP	NP	Steroids used in 31 patients	Not stated		6 (54.5)
Yechoor et al[70]	1983–1994	22–48 years	24	NP	NP	NP	NP	NP	Steroids used in 38% of patients	Median duration 9 months		9 (37.5) (6 HIV+)
Schoeman et al[84 §]	1994–1996	0–13 years	61	20 mg/kg	20 mg/kg	40 mg/kg	–	–	Steroids used in 30 children	6 months		2 (3.3)
Porkert et al[71]	1984–1995	6 months – 84 years	22 (8/15 HIVP)	NP	NP	NP	NP	NP	Steroids used in 47% of patients	At least 1 year		10 (45.5)
Donald et al[72 §]	1991–1994	Median age 38months	52	20 mg/kg	20 mg/kg	40 mg/kg	–	–	Prednisone used in 48% of patients	6 months	10 (19.2)	3 (5.8)
Hosoğlu et al[73]	1985–1996	14–67 years.	31	300 mg	600 mg	1500 mg	1 g	25/15 mg/kg**	Prednisolone given to all stage III patients	At least 9 months	8 (25.9)	4 (12. 9)

Yaramiş et al[74]	1988–1996	3 months–15 years	120	10–15 mg/kg	15–20 mg/kg	25–35 mg/kg	20–25 mg/kg		Dexamethasone 0.3–0.5 mg/kg given to all patients	12 months	31 (26)	14 (12)
Farinha et al[26]	1977–1997	Mean age 3.7 years (8 months–16 years)	10	NP	NP	NP	NP	NP	Steroids use uncertain	12–24 months		3 (30%)
Katrak et al[75]	1992–1997	23–57 years	18 (HIVP, ARV not given)	300 mg	450–600 mg	1000–1500 mg	800–1000 mg	–	Not used	uncertain	6 (33)	7 (38.9) (7 HIV+)
Katrak et al[75]	1992–1997	23–57 years	17 (HIVN)	300 mg	450–600 mg	1000–1500 mg	800–1000 mg	–	Not used	uncertain	11 (64.7)	0
Paganini et al[76]	1989–1995	1 month–13 years	16	10 mg/kg	10 mg/kg	25–30 mg/kg		–	Steroids used in 55% of children	Mean duration 10 months	10 (62.5)	1 (6)
Lu et al[77]	1995–1999	16–83 years	20 (HIVN)	300 mg	450 mg	1500 mg	–	800 mg	Steroids used in 47% of patients	Uncertain	9 (45)	3 (15)
Hosoglu et al[78] *	1985–1997	18–83 years	128	300 mg	600 mg	1500 mg	1 g	25/15 mg/kg**	Steroids used in 55% of patients	At least 9 months	43 (25.8)	31 (18.6)
Thwaites et al[79]	1997–2000	Median 33 years. 90% 16–64	24 (20% HIVP)	5 mg/kg	10 mg/kg	30 mg/kg	20 mg/kg	–	Corticosteroids not used	9 months		6 (25)
Wang et al[80]	1994–1999	16–80 years	18 (12% HIVP)	NP	NP	NP	–	NP	Steroids used in 23% of patients	Median 12 months (6–18 months)	13 (72.2)	1 (5.6)
Cagatay et al[81]	1991–2002	Mean 33.9 years (16–60)	15 (HIV?)	300 mg	600 mg	2000 mg	1500 mg	–	–	12 months	5 (33.3)	0
Thwaites et al[3]	2001–2003	Median 35 years. (15–84)	125 (20%HIVP)	5 mg/kg	10 mg/kg	25 mg/kg	20 mg/kg	20 mg/kg	Corticosteroids not used	9 months	11 (8.8)†	50 (40)
Thwaites et al[3]	2001–2003	Median 36 years. (15–88	122 (16%HIVP)	5 mg/kg	10 mg/kg	25 mg/kg	20 mg/kg	20 mg/kg	Dexamethasone 0.4 mg/kg and tapered	9 months	19 (15.6)†	38 (31.1)
Faella et al[82]	1986–2001	Median 85 months. (8–160)	10 (HIVN)	5 mg/kg	10 mg/kg	–	20 mg/kg	–	Dexamethasone 0.3 mg/kg	10–18 months	1 (10)	0

EMB = ethambutol, HIVN = human immunodeficiency virus-uninfected, HIVP = human immunodeficiency virus-infected, INH = isoniazid, LOC = level of consciousness. NP = Not provided. RMP = rifampicin, SM = streptomycin.

* Treatment is not specifically stated; it is presumed to be similar to that in the author's previous paper.

† Severe disability.

§ All patients also received ETH 20 mg/kg for 6 months.

** 25/15 mg/kg given for the first two months followed by 15 mg/kg.

Table 6
Results of treatment of TBM stage III with RMP containing regimens.

Authors	Period	Population	N	INH	RMP	PZA	SM	EMB	Corticosteroids	Duration	Sequelae	Mortality
Rahajoe et al[44]	1977–1978	Children 5 months–11 years	14	20 mg/kg	10–15 mg/kg	–	30–50 mg/kg	–	All children received corticosteroids	18 months	7 (50)	6 (42.9)
Sunakorn et al[57]	1977–1979	Children	1	15 mg/kg	15 mg/kg	–	20–40 mg/kg	15 mg/kg	–	6 months	0	0
Bateman et al[58]	1970–1980	2–74 years	15	NP	NP	NP	NP	NP	Used in 84% of patients	9–24 months	7 (46.7)	7(46.7)
Ramachandran et al[59]	1977–1981	Children 1–12 years	15	12 mg/kg	12 mg/kg	30 mg/kg	40 mg/kg	17.5 mg/kg	Steroids used in all children	12 months	3 (20)	11 (73.3)
Phuapradit & Vejjajiva[60]	1983–1984	Adults 17–76 years	5	300 mg	600/450 mg	1500 mg	750–1000 mg	–	Prednisolone	9 months	1 (20)	2 (40)
Doğany et al[45]	1982–1988	Adults	9	600 mg	600 mg	–	1 g	–	Prednisolone 1 mg/kg or dexamethasone for raised intracranial pressure.	12 months	4 (44.4)	2 (22.2)
Visudhiphan & Chiemchanya[61]	1979–1985	Children 7 months–14 years	19	10–15 m/kg	15 mg/kg	–	–	–	Prednisolone 2 mg/kg	12 months	8 (42.1)	3 (15.8)
Alarcón et al[62]	1986–1989	11 months – 70 years.	14	10 mg/kg	15 mg/kg	30 mg/kg	–	–	Prednisone 1–3 mg/kg	6 months	1 (7.1%)	9 (64.3)
Humphries et al[63]	1961–1984	2 months–14 years	72	NP Used in all children	NP Used in 84% of children	NP Used in 44% of children	NP Used in 84% of children	NP Used in 47% of children	Hydrocortisone used in 73% of children	Mean 24 months	45 (62.5)	12 (16.7)
Waecker & Connor[64]	1976–1989	6–65 months	17	NP Used in all children	NP Used in 87% of children	NP Used in 6.7% of children	NP Used in 38% of children	NP Used in 53% of children	Steroids used in 83% of children	12 months	15 (88.2)	1 (5.9)
Chotmongkol[65]	1988–1990	16–61 years	12	300 mg	600/450 mg	1500 mg	750 mg	–	Prednisolone used for those depressed LOC	6 months	3 (25%)	3 (25)
Jacobs et al[85]	1984–1990	Children	12	15 mg/kg	20 mg/kg	30 mg/kg	40 mg/kg	–	Dexamthasone	6 months	1 (8.3)	5 (41.7)
Altanbaşak et al[66]	1988–1992	6 months–13 years	20	15–20 mg/kg max 500 mg	15–20 mg/kg max 600 mg	–	20–40 mg/kg max 1 g	–	Dexamthasone	18–24 months	9 (45)	11 (55)
Doer et al[67]	1984–1994	3 months–15 years	9	10–15 mg/kg	10–20 mg/kg	25–35 mg/kg	20–25 mg/kg	15 mg/kg in some patients	Prednisone, prednisolone or dexamthasone	9–20 months	2 (22.2)	4 (44.4)
Doğanay et al[68]	1989–1993	Adults >15 years	31	300 mg	600 mg	1500 mg	1 g	NP	Prednisolone for all strage III cases	8–16 months		5 (16.1)%
Yechoor et al[70]	1983–1994	22–48 years	3	NP	NP	NP	NP	NP	Steroids used in 38% of patients	Median duration 9 months		2 (66.7) (1 HIV+)
Verdon et al[69]	1982–1983	18–83 years	29 (20.8% HIVP)	NP	NP	NP	NP	NP	Steroids used in 31 patients	Not stated		24 (82.8)
Schoeman et al[84 c]	1994–1996	0–13 years	48	20 mg/kg	20 mg/kg	40 mg/kg	–		Steroids used in 24 children	6 months		15 (31.3)
Donald et al 1998[72 §]	1991–1994	Median age 17 months	39	20 mg/kg	20 mg/kg	40 mg/kg			Prednisone used in 48% of patients	6 months	12 (30.8)	10 (25.6)
Hosoğlu et al[73]	1985–1996	14–67 years.	54	300 mg	600 mg	1500 mg	1 g	25/15 mg/kg**	Prednisolone given to all stage III patients	At least 9 months	10 (18.5)	37 (68.5)

Yaramiş et al[74]	1988–1996	3 months–15 years.	72	10–15 mg/kg	15–20 mg/kg	25–35 mg/kg	20–25 mg/kg		Dexamethasone 0.3–0.5 mg/kg given to all patients	12 months	27 (38%)	35 (49)
Farinha et al[26]	1977–1997	8 months–16 years	21	NP	NP	NP	NP	NP	Steroids use uncertain	12–24 months	11/14 (78)	5 (23.8)
Katrak et al[75]	1992–1997	23–57 years (HIVP) ARV not given	1 (HIVP, No ARV)	300 mg	450–600 mg	1000–1500 mg	800–1000 mg	–	Not used	uncertain	–	1 (100)
Katrak et al[75]	1992–1997	23–57 years (HIVN)	3 (HIVN)	300 mg	450–600 mg	1000–1500 mg	800–1000 mg	–	Not used	uncertain	–	3 (100)
Paganini et al[76]	1989–1995	1 month–13 years	6 (HIVN)	10 mg/kg	10 mg/kg	25–30 mg/kg		–	Steroids used in 55% of children	Mean duration 10 months	4 (66.7)	2(33.3)
Lu et al[77]	1995–1999	16–83 years	3 (HIVN)	300 mg	450 mg	1500 mg	–	800 mg	Steroids used in 47% of patients	Uncertain	1 (33.3)	2 (66.7)
Hosoglu et al[78] *	1985–1997	18–83 years	128	300 mg	600 mg	1500 mg	1 g	25/15 mg/kg**	Steroids used in 55% of patients	At least 9 months	19 (14.8)	57 (44.5)
Thwaites et al[79]	1997–2000	Median 33 years. 90% 16–64	24 (20% HIVP)	5 mg/kg	10 mg/kg	30 mg/kg	20 mg/kg		Corticosteroids not used	9 months		17 (70.8)
Wang et al[80]	1994–1999	16–80 years	2 (12.2% HIVP)	NP	NP	NP	–	NP	Steroids used in 23% of patients	Median 12 months (6–18 months)	1 (50)	1 (50)
Cagatay et al[81]	1991–2002	Mean 33.9 years (16–60)	10 (7%HIVP)	300 mg	600 mg	2000 mg	1500 mg			12 months	7 (70)	3 (30)
Thwaites et al[3]	2001–2003	Median 35 years. (15–84)	60 (20%HIVP)	5 mg/kg	10 mg/kg	25 mg/kg	20 mg/kg	20 mg/kg	Corticosteroids not used	9 months	7 (11.7)†	36 (60)
Thwaites et al[3]	2001–2003	Median 36 years. (15–88	62 (16%HIVP)	5 mg/kg	10 mg/kg	25 mg/kg	20 mg/kg	20 mg/kg	Dexamethasone 0.4 mg/kg and tapered	9 months	11 (17.7)†	34 (54.8)
Faella et al[82]	1986–2001	Median 85 months. (8–160)	17 (HIVN)	5 mg/kg	10 mg/kg	–	20 mg/kg	–	Dexamethasone 0.3 mg/kg	10–18 months	5 (29.4)	4 (23.5)

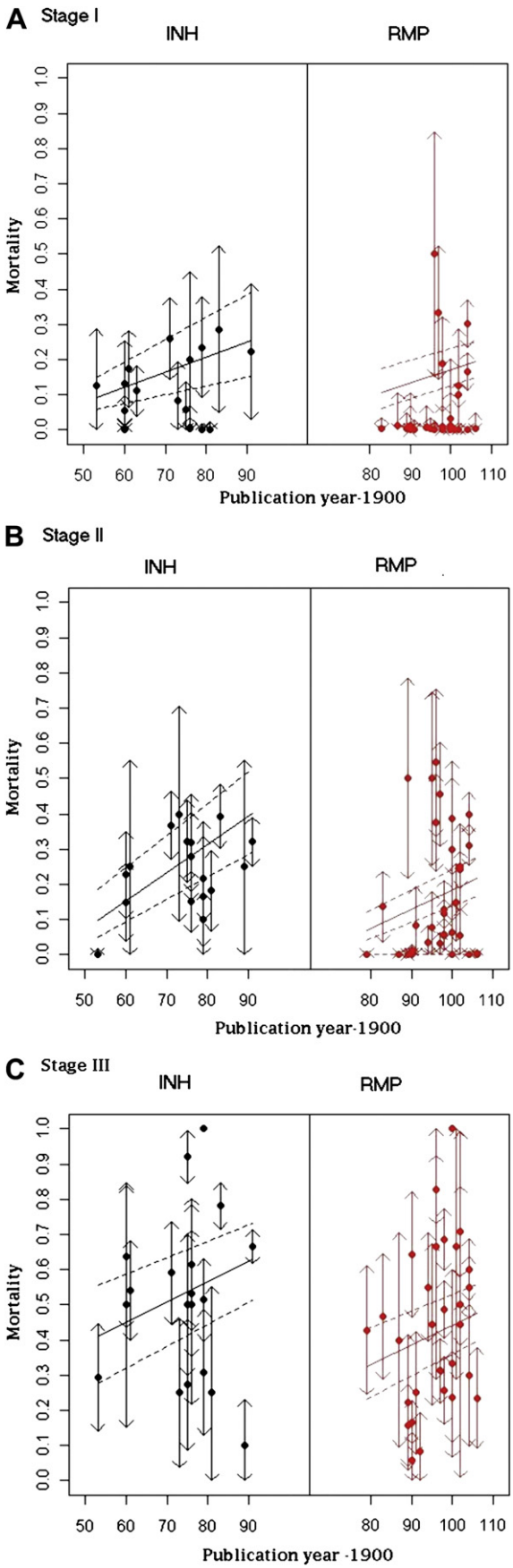
EMB = ethambutol, HIVN = human immunodeficiency virus-uninfected, HIVP = human immunodeficiency virus-infected, INH = isoniazid, LOC = level of consciousness. NP = Not provided. RMP = rifampicin, SM = streptomycin.

* Treatment is not specifically stated; it is presumed to be similar to that in the author's previous paper.

† Severe disability.

§ All patients also received ETH 20 mg/kg for 6 months.

** 25/15 mg/kg given for the first two months followed by 15 mg/kg.



considered in constructing regimens for the treatment of TBM.[125] More recently a similar course of events was described in a patient treated with INH, RMP, PZA and EMB for extra-pulmonary tuberculosis affecting several sites, but also not, initially, the CNS.[126] This patient also had an INH-resistant isolate and developed TBM while on the continuation phase of treatment.

The threat of INH resistance and multidrug resistance has prompted some clinicians to routinely use a regimen containing ETH and high-dosage INH.[72] If INH resistance should be due to a *Kat*G mutation it is likely that the isolate will still be susceptible to ETH and if the mutation involves the *Inh*A gene then high-dosage INH may still be effective.

Because of the limited number of drugs available MDR increases the mortality of TBM considerably, particularly in the presence of HIV.[4,127–137] The paper of Daikos et al. is particularly interesting providing a precise description of treatment regimens used to manage MDR tuberculosis *not* involving the CNS in 8 HIV-infected adult patients in Miami, Florida, USA, who then went on to develop TBM.[134] Each regimen included at least two drugs to which the isolate was sensitive. One patient was lost to follow-up, and the remainder died. All the patients received INH and PZA accompanied by RMP in five patients, EMB in five patients, SM in four, amikacin in two, cycloserine in four, ciprofloxacin in two patients and PAS in one. The susceptibility of the isolates to PZA is not reported, but the outcome suggests that the remaining drugs were insufficient to prevent or control CNS tuberculosis. INH might still have had some value if the MIC of the isolate was relatively low; RMP would probably have been without effect, EMB, SM and AMK have very limited CSF entry and ciprofloxacin, is the least active of the fluoroquinolones and in the CSF would reach at most, 30% of serum concentrations. Treatment (and prevention of TBM in these cases) might thus have depended almost entirely on PZA (if the isolates were still susceptible) assisted by CS in some cases. The events described in this paper serve as a grave warning of the consequences of MDR for TBM management in both immunocompetent and immunosuppressed individuals.

A number of other publications provide similar evidence of the incidence and consequences of MDR TBM.[135–141]

The influence of HIV infection

From 1990 onwards an increasing number of papers described the occurrence of TBM in HIV-infected adults and children and a significantly higher mortality was reported in those HIV-infected in the absence of anti-retroviral treatment.[127,128]

Although a number of papers present data related to the morbidity and mortality associated with TBM in HIV-infected individuals, there is little documented evidence regarding the length of treatment required in such patients; the most recent edition of the WHO guidelines for tuberculosis treatment, while acknowledging that some studies have found lower relapse rates amongst HIV-infected tuberculosis patients treated with RMP containing regimens for 8 months or longer recommend that HIV-infected patients “should receive at least the same duration of therapy as HIV-negative patients”.[142] The complications caused by the effect of RMP on concentrations of anti-retroviral agents and

Figure 1. Mortality of adults and children receiving isoniazid (INH) based regimens compared to that for rifampicin (RMP) and pyrazinamide based regimens at stage I tuberculous meningitis (1A), stage II tuberculous meningitis (1B) and stage III tuberculous meningitis (1C); data from Tables 1 and 4 (1A), Tables 2 and 5 (1B) and Tables 3 and 6 (1C). The limits shown with each plotted point are ±1.4 (standard error); the factor 1.4 is chosen so that two observed mortality rates differ significantly at level 0.05 if the limit intervals do not overlap. The unbroken fitted lines represent estimated expected values and the dotted lines 95% confidence intervals.

Table 7
Mortality (%) as result of tuberculous meningitis in case series describing both adults and children and only children associated with regimens of isoniazid (INH), streptomycin and para-amino salicylic acid (INH regimens) compared to those of isoniazid, and rifampicin (RMP) accompanied by pyrazinamide and ethambutol in most cases (RMP regimens).

Stage	Regimen	Adults and children	SE	P	Children	SE	P
I	INH	12.4	3.0	0.412	10.2	2.7	<0.001
	RMP	9.7	1.6		0.0	0.0	
II	INH	25.2	5.3	0.621	22.3	5.1	<0.001
	RMP	22.2	3.2		5.9	1.4	
III	INH	55.0	7.8	0.908	49.4	6.0	0.006
	RMP	56.0	5.2		28.2	4.7	

This analysis used the recorded mortality in the various studies as a response variable and the mortality was taken to vary randomly from study to study.

other drugs and the potential effects on the efficacy of TBM treatment should RMP be replaced by rifabutin or other drugs remain to be explored.

Regimens proposed by various professional bodies and national committees include

European Respiratory Society, the World Health Organization and the International Union against Tuberculosis and Lung Disease Europe Region.[143] For new cases of severe forms of extra-pulmonary tuberculosis INH, RMP, PZA daily or three times weekly followed by four months of INH and RMP, either daily or three times weekly, is recommended. A continuation phase of six months INH and EMB is recommended only when RMP is not tolerated. It is specifically noted that a daily dosage of INH in excess of 10 mg/kg used to treat children with TBM or disseminated TB may be associated with hepatotoxicity. This recommendation can be traced to the experience of Ramachandran et al. working in Chennai, India, an area acknowledged to have a particularly high incidence of infectious hepatitis.[59]

World Health Organization 2003: INH, RMP, PZA and SM for two months followed by INH and RMP for four months.[144]

American Academy of Pediatrics 2003: INH, RMP, PZA, (SM or ETH) for two months followed by INH and RMP for 7–10 months.[145]

American Thoracic Society, CDC, and Infectious Diseases Society of America 2003: INH, RMP, PZA and EMB for two months followed by INH and RMP for 7–10 months.[146]

Deutsches Zentralkomitee zur Bekämpfung der Tuberkulose 2001: INH, RMP, PZA and EMB for 2–3 months followed by INH and RMP for 9–10 months.[147]

World Health Organization. Guidance for national programmes on the management of tuberculosis in children 2006: INH, RMP, PZA and SM for two months followed by INH and RMP for four months.[148] In the main body of this document the standard regimen of two months of INH, RMP, PZA and SM, followed by four months of INH and RMP is recommended. In annexure 4 the treatment of TBM is discussed at a greater length and alternative regimens of INH. RMP, PZA and SM (or ETH) for two months followed by INH and RMP for four months or six months of INH, RMP, PZA and ETH mentioned as being recommended by other groups.

Brazilian Thoracic Association: Guidelines on Tuberculosis 2009: An intensive two month phase of INH, RMP, PZA and EMB followed by seven months of INH and RMP is recommended for adults, but for children an intensive 2-month phase of three drugs, INH, RMP and PZA followed by seven months of INH and RMP.[149]

British Infection Society guidelines for the diagnosis and treatment of tuberculosis of the central nervous system in adults and children 2009: The recommended first-line treatment for all forms of central nervous system tuberculosis is INH and RMP for 12 months and PZA and EMB for two months. All patients should be treated for a minimum of 12 months. The following dosages are recommended for children: INH 10–20 mg/kg (maximum 500 mg); RMP 10–20 mg/kg (maximum 600 mg); PZA 30–35 mg/kg (maximum 2 g) EMB 15–20 mg/kg (maximum 1 g); and for adults: INH 300 mg; RMP 450 mg (bodyweight $<$ 50 kg) and 600 mg (bodyweight $\geq$ 50 kg); PZA 1.5 g (bodyweight $>$ 50 kg) and 2.0 g (bodyweight $\geq$ 50 kg); and EMB 15 mg/kg.[150]

World Health Organization 2009: Chapter 8 of this report deals specifically with extra-pulmonary tuberculosis. It is recommended that pulmonary and extra-pulmonary tuberculosis should be treated with the same regimen, ie INH, RMP, PZA and SM for two months followed by INH and RMP for four months, but it is added that "some experts recommend 9–12 months of treatment for TB meningitis…".[142]

Indian Academy of Pediatrics Working Group on Tuberculosis 2010: TBM is classified as a severe form of extra-pulmonary tuberculosis and an intensive phase of INH, RMP, PZA and SM or EMB recommended followed by a continuation phase of INH and RMP for 6–7-months. It is recommended that this regimen be given thrice weekly under supervision, but that, if supervision is not possible, the regimen should be prescribed daily.[151]

Regimens used or recommended by individual groups of authors

Ellard et al., 1993: INH 10 mg/kg, RMP 10 mg/kg, PZA 35 mg/kg all given for 9–12 months with SM 20 mg/kg for the first 2–3 months. In event of a serious risk of INH resistance ETH (dosage not given) is added.[92]

Donald et al., 1998 (*children*): INH 20 mg/kg, RMP 20 mg/kg, PZA 40 mg/kg, ETH 40 mg/kg, all given for six months.[72]

Thwaites et al., 2004: INH 5 mg/kg, RMP 10 mg/kg, PZA 25 mg/kg, SM 20 mg/kg all given for three months and followed by INH, RMP and PZA all at the same dosages for six months. EMB 20 mg/kg is substituted for SM in HIV-infected patients.[3]

Conclusions and recommendations

As illustrated by this review, TBM remains a devastating disease despite the use of antituberculosis drugs and regimens effective in other forms of tuberculosis. It is of interest that the introduction of RMP and PZA into antituberculosis regimens appears to have had little effect on disease mortality in adults, but has reduced mortality in children. This could be due to the higher dosages of antituberculosis drugs used by many paediatricians, but the nature of the disease in adults may also play a role. It is noteworthy that even in patients presenting at stage I TBM disease, deterioration, and death, may still occur. As with other forms of bacterial meningitis antituberculosis treatment should be started as soon as the diagnosis of TBM is considered and higher dosages of drugs, particularly RMP, may be advantageous. As noted more than 50 years ago it is also likely that a greater understanding of the causes of vasculitis and accompanying brain damage will be needed before appropriate measures to manage and prevent these complications will be possible.[1]

In evaluating regimens for the management of pulmonary tuberculosis relapse rates of 5% are often considered satisfactory. In the case of TBM it must be asked whether any risk of relapse is acceptable and whether the price of continuing therapy to nine months or 12 months in what would be a relatively small number of patients in a particular area, is not acceptable? In situations where the directly observed treatment and follow-up, *after treatment completion*, is impeccable, six months treatment duration is probably satisfactory. In situations where treatment supervision and follow-up is questionable it may be better practice to prolong

treatment to nine or 12 months, although this might amount to 'overkill'.

From the papers reviewed it is clear that most regimens proposed for the chemotherapy of fully drug-sensitive TBM will nearly always include INH, RMP, PZA and either EMB or SM. The choice of drugs is also constrained by the limited number of "essential drugs" available in many parts of the world where TBM is common. It should be noted that the most recent WHO guidelines no longer recommend EMB for the treatment of TBM and state that it should be replaced by SM.[142] Nonetheless, as indicated in this review the contribution of SM and EMB to the treatment of TBM is probably limited. Taking into account the restricted options available the following regimen is recommended for the treatment of TBM in adults and children in areas where drug resistance is not a serious problem and treatment compliance is assured:

Daily INH, RMP, PZA, SM (or EMB in the event SM cannot be used) for two months followed by INH and RMP for four months. When compliance cannot be assured the continuation phase should be prolonged to seven months.

The following dosages of the essential antituberculosis drugs are recommended:

Daily drug dosages for children	Daily drug dosages for adults
INH 10 mg/kg (range 6–15 mg/kg)	% mg/kg (range 4–6)
RMP 15 mg/kg (range 10–20 mg/kg)	10 mg/kg (range 8–12)
PZA 35 mg/kg (range 30–40 mg/kg)	25 mg/kg (range 20–30)
SM 17.5 mg/kg (range 15–20 mg/kg)	15 mg/kg (range 12–18)
EMB 20 mg/kg (range 15–25 mg/kg)	15 mg/kg (range 15–20)

In all instances the higher end of the dosage range should be used to treat children. From approximately the age of 12 years adult dosages can be applied. The same regimen, with the necessary adjustment of dosages is also recommended for the treatment of adults.

In areas where INH resistance occurs in a significant proportion of cases (>4% of primary infections) consideration should be given to replacing SM (or EMB) with ETH and continuing PZA until treatment completion. Should there be any reason to suspect MDR tuberculosis there should be little hesitation in adding OFX (20 mg/kg) or another fluoroquinolone and CS (15–20 mg/kg) to the regimen until confirmation of susceptibility of the responsible isolate is obtained.

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