

# Evidence Search ServiceResults of your search request

## Intensified antibiotic treatment of tuberculous meningitis

**ID of request:** 13495
**Date of request:** 4th June, 2018
**Date of completion:** 6th July, 2018

If you would like to request any articles or any further help, please contact:  Tom Roper at tom.roper@bsuh.nhs.uk

Please acknowledge this work in any resulting paper or presentation as: Evidence search: Intensified antibiotic treatment of tuberculous meningitis. Tom Roper. ( 6th July, 2018). BRIGHTON, UK: Brighton and Sussex Library and Knowledge Service.

**Sources searched**
EMBASE (87)
MEDLINE (155)

**Date range used** (5 years, 10 years): No restrictions
**Limits used** (gender, article/study type, etc.): None
**Search terms and notes** (full search strategy for database searches below):

MEDLINE and EMBASE were searched with text word and controlled vocabulary terms. Duplicates were removed, but no relevance screen undertaken. References supplied by the search requester were used to make a test set, against which iterations of the strategy could be tested.

A search of Cochrane Central located four papers, all of which were also retrieved by the MEDLINE and EMBASE searches.

Some commentary on the search strategy may be helpful. Taking MEDLINE as the examples, lines 1-3 locate the concept of tuberculous meningitis, while lines 5-7 locate antibiotic treatment. I then combined those concepts with AND and then the string intensif\*, This is the most simple form of the search and returns 11 results in MEDLINE, and exactly the same number in EMBASE.

I then added further lines to expand the concept of intensified treatment. Line 23 looks for increased doses, while lines 24 and 25 look for combinations of drugs. Lines 26 to 40 retrieve the specific drugs you mentioned, and lines 41 and 42 find other anti-tubercular treatments that might be used. The final lines bring all these together.

For more information about the resources please go to: <https://www.bsuh.nhs.uk/library/>.

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### [B. Search History](#SearchHistory)

## A. Original Research

1. **Treatment of Central Nervous System Tuberculosis**
Ahmed A. Journal of Pediatric Infectious Diseases 2018;13(2):141-152.

Central nervous system tuberculosis (CNS-TB) manifests as tuberculous meningitis, intracranial tuberculoma, or spinal tuberculous arachnoiditis. Children are disproportionately affected, with high rates of mortality and morbidity reported even in the era of treatment. Most guidelines for the treatment of drug-susceptible CNS-TB recommend 9 to 12 months of a standard regimen of isoniazid, rifampin, pyrazinamide, and ethambutol, with the adjunctive use of corticosteroids early in therapy. Recent trials have demonstrated improved outcomes with intensified regimens using nonstandard regimens or higher dosages of standard drugs. Accumulating evidence also supports shorter duration of treatment. Further investigation is warranted to identify the optimal regimen and duration of treatment for CNS-TB. Complications such as hydrocephalus may be managed medically or surgically. Although outcomes have improved with effective chemotherapy and immunomodulation of disease, prompt diagnosis and treatment in the early stages of disease remain paramount to improve prognosis.<br/>Copyright &#xa9; 2018 by Georg Thieme Verlag KG, Stuttgart.New York.

1. **Clinical Outcomes of Patients With Drug-Resistant Tuberculous Meningitis Treated With an Intensified Antituberculosis Regimen.**
Heemskerk A. Dorothee Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 2017;65(1):20-28.

BackgroundDrug-resistant tuberculous meningitis (TBM) is difficult to diagnose and treat. Mortality is high and optimal treatment is unknown. We compared clinical outcomes of drug-resistant and -susceptible TBM treated with either standard or intensified antituberculosis treatment.MethodsWe analyzed the influence of Mycobacterium tuberculosis drug resistance on the outcomes of patients with TBM enrolled into a randomized controlled trial comparing a standard, 9-month antituberculosis regimen (containing rifampicin 10 mg/kg/day) with an intensified regimen with higher-dose rifampicin (15 mg/kg/day) and levofloxacin (20 mg/kg/day) for the first 8 weeks. The primary endpoint of the trial was 9-month survival. In this subgroup analysis, resistance categories were predefined as multidrug resistant (MDR), isoniazid resistant, rifampicin susceptible (INH-R), and susceptible to rifampicin and isoniazid (INH-S + RIF-S). Outcome by resistance categories and response to intensified treatment were compared and estimated by Cox regression.ResultsOf 817 randomized patients, 322 had a known drug resistance profile. INH-R was found in 86 (26.7%) patients, MDR in 15 (4.7%) patients, rifampicin monoresistance in 1 patient (0.3%), and INH-S + RIF-S in 220 (68.3%) patients. Multivariable regression showed that MDR (hazard ratio [HR], 5.91 [95% confidence interval {CI}, 3.00-11.6]), P < .001), was an independent predictor of death. INH-R had a significant association with the combined outcome of new neurological events or death (HR, 1.58 [95% CI, 1.11-2.23]). Adjusted Cox regression, corrected for treatment adjustments, showed that intensified treatment was significantly associated with improved survival (HR, 0.34 [95% CI, .15-.76], P = .01) in INH-R TBM.ConclusionsEarly intensified treatment improved survival in patients with INH-R TBM. Targeted regimens for drug-resistant TBM should be further explored.Clinical Trials RegistrationISRCTN61649292.

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1. **Intrathecal Isoniazid for Refractory Tuberculous Meningitis with Cerebral Infarction.**
Nakatani Yuko Internal medicine (Tokyo, Japan) 2017;56(8):953-957.

A 30-year-old Vietnamese woman, about 19 weeks pregnant, was admitted for acute cerebral infarction with stenosis of the left middle cerebral artery (LMCA), tuberculous meningitis, and miliary tuberculosis. Treatment with heparin, quadruple anti-tuberculosis therapy, and dexamethasone afforded prompt symptomatic improvement. However, she delivered a stillbirth, after which there was recurrence of acute cerebral infarction with LMCA occlusion, sinus thrombosis, and cranial base inflammation. A thrice-weekly 100 mg dose of intrathecal isoniazid (INH) improved the signs of meningeal inflammation. The patient was discharged ambulatory after 7 months. In refractory tuberculous meningitis, multimodal therapy with intrathecal INH and steroids should be considered.

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1. **Severe headache, neck pain, intermittent cough · Dx?**
Lyon Claudia The Journal of family practice 2017;66(5):316-318.

A 32-year-old Chinese woman sought care from our family medicine clinic because she had a headache, neck pain, and an intermittent cough that had produced white sputum for 7 days. She described the headache as severe and pressure-like, and said that it had progressively worsened over the previous 3 weeks, coinciding with her first trip outside of China to the United States. The patient indicated that she also had occasional vomiting, dizziness, a low-grade fever, chills, night sweats, and increasing fatigue.

1. **Tuberculous meningitis**
Wilkinson R.J. Nature Reviews Neurology 2017;13(10):581-598.

Tuberculosis remains a global health problem, with an estimated 10.4 million cases and 1.8 million deaths resulting from the disease in 2015. The most lethal and disabling form of tuberculosis is tuberculous meningitis (TBM), for which more than 100,000 new cases are estimated to occur per year. In patients who are co-infected with HIV-1, TBM has a mortality approaching 50%. Study of TBM pathogenesis is hampered by a lack of experimental models that recapitulate all the features of the human disease. Diagnosis of TBM is often delayed by the insensitive and lengthy culture technique required for disease confirmation. Antibiotic regimens for TBM are based on those used to treat pulmonary tuberculosis, which probably results in suboptimal drug levels in the cerebrospinal fluid, owing to poor blood-brain barrier penetrance. The role of adjunctive anti-inflammatory, host-directed therapies-including corticosteroids, aspirin and thalidomide-has not been extensively explored. To address this deficit, two expert meetings were held in 2009 and 2015 to share findings and define research priorities. This Review summarizes historical and current research into TBM and identifies important gaps in our knowledge. We will discuss advances in the understanding of inflammation in TBM and its potential modulation; vascular and hypoxia-mediated tissue injury; the role of intensified antibiotic treatment; and the importance of rapid and accurate diagnostics and supportive care in TBM.<br/>Copyright &#xa9; 2017 Macmillan Publishers Limited, part of Springer Nature. All rights reserved.

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1. **Tuberculous Meningitis in Children and Adults: New Insights for an Ancient Foe.**
Mezochow Alyssa Current neurology and neuroscience reports 2017;17(11):85-.

PURPOSE OF REVIEWTuberculous meningitis is the most devastating manifestation of infection with Mycobacterium tuberculosis and represents a medical emergency. Approximately one half of tuberculous meningitis patients die or suffer severe neurologic disability. The goal of this review will be to review the pathogenic, clinical, and radiologic features of tuberculous meningitis and to highlight recent advancements in translational and clinical science.RECENT FINDINGSPharmacologic therapy includes combination anti-tuberculosis drug regimens and adjunctive corticosteroids. It is becoming clear that a successful treatment outcome depends on an immune response that is neither too weak nor overly robust, and genetic determinants of this immune response may identify which patients will benefit from adjunctive corticosteroids. Recent clinical trials of intensified anti-tuberculosis treatment regimens conducted in Indonesia and Vietnam, motivated by the pharmacologic challenges of treating M. tuberculosis infections of the central nervous system, have yielded conflicting results regarding the survival benefit of intensified treatment regimens. More consistent findings have been observed regarding the relationship between initial anti-tuberculosis drug resistance and mortality among tuberculous meningitis patients. Prompt initiation of anti-tuberculosis treatment for all suspected cases remains a key aspect of management. Priorities for research include the improvement of diagnostic testing strategies and the optimization of host-directed and anti-tuberculosis therapies.

1. **Use of continuous high-frequency oscillation (CHFO) and continuous positive expiratory pressure (CPEP) therapy in a patient admitted for COPD exacerbation: Quality improvement and unexpected benefit**
Landon C. American Journal of Respiratory and Critical Care Medicine 2017;195:-.

INTRODUCTION: Continuous high-frequency oscillation (CHFO) and continuous positive expiratory pressure (CPEP) therapies have been shown to be effective in treatment of atelectasis and pulmonary secretion clearance. The MetaNeb<sup></sup> System delivers both therapies and aerosol medication to improve mucus clearance and to recruit obstructed bronchi and alveoli. A Quality Improvement evaluation was undertaken at our institution to evaluate tolerance, effectiveness of the therapy, and patient selection. Admitting diagnoses were diverse and included a number of patients with COPD. In one particular case of COPD an additional capability of MetaNeb Therapy emerged. CASE REPORT: The patient is a 60-year-old male with a history of GOLD 2 COPD (FEV1 57%) was brought in by his wife for a change in level of consciousness which she associated with exacerbation of COPD. CT of the chest revealed emphysematous changes consistent with COPD with areas of cavitation and lower lobe atelectasis, head CT revealed tuberculomas consistent with tuberculous meningitis and abdominal CT showed liver cavitary lesions. The patient's initial sputum culture was not positive for multidrug-resistant tuberculosis (MDRTB) and the patient was placed on Levaquin, INH, and Rifampin. The patient was initially ordered on EZPAP therapy, but was unable to follow directions and coordinate the therapy. MetaNeb therapy with albuterol ordered along with his COPD medications. Follow-up CXR showed significant improvement in the lower lobe atelectasis. Following initiation of MetaNeb therapy, additional sputum samples were obtained which resulted in 3+ positive smear for MDRTB. Therapy was modified to streptomycin, ethambutol, and PZA. The patient remains smear positive on day 195. DISCUSSION: The MetaNeb Therapy led to an effective intervention in a patient admitted for a severe COPD exacerbation associated with tuberculosis infection. It provided effective lung expansion to improve atelectasis and prevent possible need for intubation. In addition, the clinical decision for the patient's initial ninety-day antibiotic course was hampered by the lack of appropriate sputum induction to provide a sufficient sample to identify the correct organism. However, subsequent utilization of MetaNeb allowed for sufficient sputum collection and proper diagnosis. If done earlier, it may have prevented a prolonged stay by establishing the correct medication regimen from the beginning. CHFO and CPEP therapies are safe techniques which may prevent deterioration in patients with atelectasis who are at risk for further pulmonary complications and possible intubation. Consideration of this therapy to mobilize secretions in preparation for sputum induction procedures may be warranted. [Image Presented].

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1. **A Clinical Study of Miliary Brain Tuberculomas in China.**
Yang Ming Japanese journal of infectious diseases 2016;69(3):231-235.

Brain tuberculomas can exhibit many different clinical and radiological patterns. However, disseminated or miliary brain tuberculomas are very rare. Miliary brain tuberculomas have specific clinical prognostic implications. Seven patients diagnosed with miliary brain tuberculomas between December 2004 and August 2012 were evaluated retrospectively. Their clinical features, cranial magnetic resonance imaging (MRI) characteristics, treatments, and outcomes were reviewed. The median patient age was 42 years (range, 22-66 years). Six patients presented with fever, 5 with headache, 4 with papilledema, and 3 with diplopia. MRI studies revealed multiple brain lesions. MRI showed 20-50 lesions at the same level. These lesions measured approximately 2-4 mm in diameter and exhibited ring or nodular enhancement after gadolinium injection. All patients began to recover within 2 weeks of initiating antitubercular therapy (ATT). The number of lesions visible on MRI scans was halved within a month, and all lesions had healed without sequelae after 18 months of regular ATT. Miliary brain tuberculoma is a rare form of central nervous system tuberculosis. Some special characteristics of miliary brain tuberculomas are as follows: First, the presence of mild atypical clinical manifestations and almost normal laboratory findings; second, severe radiological features and 20-50 lesions at the same level on MRI scans; and third, a good response to standard ATT. Finally, they are benign; for instance, no patients died in our study. Early diagnosis and treatment can result in full recovery.

1. **Diagnosis of mycobacterial infections based on acid-fast bacilli test and bacterial growth time and implications on treatment and disease outcome**
Riello F.N. BMC Infectious Diseases 2016;16(1):-.

Background: The establishment of therapeutic regimens for mycobacteriosis depends on the accurate identification of Mycobacterium species, and misdiagnosis can result in inappropriate treatment and increased mortality of patients. Differential diagnosis among Mycobacterium species has been made by conventional phenotypic and biochemical tests after a long culture period. Specialized molecular diagnostics of mycobacteria allows rapid detection and species identification; however, such tests are not available in public health programs. Our aim was to demonstrate the clinical implications of erroneous diagnosis by performing molecular genotyping of mycobacterial infections in patients that were diagnosed based on symptoms, culture and bacilloscopy. Methods: Culture samples of mycobacterial infections from 55 patients clinically diagnosed as tuberculosis in 2013 and 2014, based on conventional methods, were identified by PCR-RFLP and results are discussed. Results: We have confirmed 35 (63.6 %) positive samples as M. tuberculosis, but 18 (32.7 %) were identified as non-tuberculous mycobacteria (M. avium type 1, M. avium type 2, M. kansasii type 1 type 1, M. mucogenicum, M. chelonae, M. terrae type 3, and 1 unknown RFLP pattern) and two were negative. Regarding clinical diagnosis, 61.8 % (34/55) was classified as pulmonary tuberculosis. It is important to emphasize that 36.4 % (20/55) of samples were misdiagnosed by conventional methods, and 11 (61.1 %) of the HIV positive patients (18/55) were NTMcoinfected. Conclusion: The identification of species in mycobacterial infections is essential for correct diagnosis and choice of treatment regimen, and misdiagnosis by conventional tools can lead to chronic disease, increased resistance and death.<br/>Copyright &#xa9; 2016 Riello et al.

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1. **Intensified Antituberculosis Therapy in Adults with Tuberculous Meningitis.**
Heemskerk A. Dorothee The New England journal of medicine 2016;374(2):124-134.

BACKGROUNDTuberculous meningitis is often lethal. Early antituberculosis treatment and adjunctive treatment with glucocorticoids improve survival, but nearly one third of patients with the condition still die. We hypothesized that intensified antituberculosis treatment would enhance the killing of intracerebral Mycobacterium tuberculosis organisms and decrease the rate of death among patients.METHODSWe performed a randomized, double-blind, placebo-controlled trial involving human immunodeficiency virus (HIV)-infected adults and HIV-uninfected adults with a clinical diagnosis of tuberculous meningitis who were admitted to one of two Vietnamese hospitals. We compared a standard, 9-month antituberculosis regimen (which included 10 mg of rifampin per kilogram of body weight per day) with an intensified regimen that included higher-dose rifampin (15 mg per kilogram per day) and levofloxacin (20 mg per kilogram per day) for the first 8 weeks of treatment. The primary outcome was death by 9 months after randomization.RESULTSA total of 817 patients (349 of whom were HIV-infected) were enrolled; 409 were randomly assigned to receive the standard regimen, and 408 were assigned to receive intensified treatment. During the 9 months of follow-up, 113 patients in the intensified-treatment group and 114 patients in the standard-treatment group died (hazard ratio, 0.94; 95% confidence interval, 0.73 to 1.22; P=0.66). There was no evidence of a significant differential effect of intensified treatment in the overall population or in any of the subgroups, with the possible exception of patients infected with isoniazid-resistant M. tuberculosis. There were also no significant differences in secondary outcomes between the treatment groups. The overall number of adverse events leading to treatment interruption did not differ significantly between the treatment groups (64 events in the standard-treatment group and 95 events in the intensified-treatment group, P=0.08).CONCLUSIONSIntensified antituberculosis treatment was not associated with a higher rate of survival among patients with tuberculous meningitis than standard treatment. (Funded by the Wellcome Trust and the Li Ka Shing Foundation; Current Controlled Trials number, ISRCTN61649292.).

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1. **Mortality in HIV-infected patients with tuberculosis treated with streptomycin and a two-week intensified regimen: Data from an HIV cohort study using inverse probability of treatment weighting**
Alvarez-Uria G. PeerJ 2016;2016(5):-.

Background. Despite the dramatic scale-up of antiretroviral therapy in low- and middle-income countries, tuberculosis (TB) is still the main cause of death among HIV-infected patients in resource-limited settings. Previous studies in patients with TB meningitis suggest that the use of higher doses of common anti-TB drugs could reduce mortality. Methods. Using clinical data from an HIV cohort study in India, we compared the mortality among HIV-infected patients diagnosed with TB according to the regimen received during the first two weeks of treatment: standard anti-tuberculosis therapy (ATT) (N = 847), intensified ATT (N = 322), and intensified ATT with streptomycin (N = 446). The intensified ATT comprised double dose of rifampicin and substitution of ethambutol with levofloxacin. Multivariate analysis was performed using Cox proportional hazard models and inverse probability of treatment weighting (IPTW) based on propensity scores. Patients with TB meningitis were excluded. Results. The use of intensified ATT alone did not improve survival. However, when streptomycin was added, the use intensified ATT was associated with reduced mortality in Cox models (adjusted hazard ratio 0.72, 95% CI [0.57-0.91]) and after IPTW (hazard ratio 0.77, 95% CI [0.67-0.96]). Other factors associated with improved survival were high serum albumin concentration, high CD4 lymphocyte cell-counts, and high glomerular filtration rates. Factors associated with increased mortality were high urea concentrations, being on antiretroviral therapy at the time of ATT initiation and high BUN/creatinine ratio. In an effect modification analysis, the survival benefits of the intensified ATT with streptomycin disappeared in patients with severe hypoalbuminemia. Conclusion. The results of this study are in accordance with a previous study from our cohort involving patients with TB meningitis, and suggest that an intensified 2-week ATT with streptomycin could reduce mortality in HIV infected patients with TB. As this is an observational study, we should be cautious about our conclusions, but given the high mortality of HIV-related TB, our findings deserve further research.<br/>Copyright &#xa9; 2016 Alvarez-Uria et al.

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1. **Pharmacokinetics and safety/tolerability of higher oral and intravenous doses of rifampicin in adult tuberculous meningitis patients.**
Yunivita Vycke International journal of antimicrobial agents 2016;48(4):415-421.

High-dose intravenous (i.v.) rifampicin improved the outcome of tuberculous meningitis (TBM) in a previous study. Unfortunately, i.v. rifampicin is not available in many high-endemic settings. This study examined exposures to and safety of higher oral rifampicin doses compared with i.v. rifampicin. Thirty adult Indonesian TBM patients were randomised to rifampicin 750 mg (ca. 17 mg/kg) orally, 900 mg (ca. 20 mg/kg) orally or 600 mg (ca. 13 mg/kg, as used previously) i.v. over 1.5 h for 14 days, combined with other TB drugs. The pharmacokinetics of rifampicin was assessed in the critical phase of TBM treatment (≤3 days after treatment initiation) and at ≥9 days. In the first days of treatment, the geometric mean (range) plasma AUC0-24 values following rifampicin 750 mg orally, 900 mg orally and 600 mg i.v. were 131.4 (38.1-275.1), 164.8 (66.9-291.2) and 145.7 (77.7-430.2) mg⋅h/L, respectively; Cmax values were 14.3 (6.1-22.2), 16.2 (5.7-28.3) and 24.7 (13.9-37.8) mg/L. CSF concentrations correlated with plasma exposures. After ≥9 days, AUC0-24 values had decreased to 100.1, 101.2 and 94.9 mg⋅h/L. Transient grade 3 ALT increases (8/30 patients) and one grade 4 ALT increase occurred, not related to rifampicin exposure. Higher oral rifampicin doses resulted in approximately similar plasma AUC0-24 but lower plasma Cmax values compared with 600 mg i.v. over 1.5 h. Exposures to rifampicin varied substantially and decreased due to autoinduction. Liver function disturbances occurred in this severely ill population. Future studies should examine even higher rifampicin doses in TBM treatment.

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1. **Safety and efficacy of additional levofloxacin in tuberculous meningitis: A randomized controlled pilot study.**
Kalita J. Tuberculosis (Edinburgh, Scotland) 2016;98:1-6.

BACKGROUNDLevofloxacin is an effective bactericidal category III antitubercular drug. There is paucity of studies comparing the role of additional levofloxacin to standard antitubercular regimen in the patients with tuberculous meningitis (TBM).AIMSTo compare the safety and efficacy of adding levofloxacin to standard four drug ATT regimen (RHZE).SUBJECTS AND METHODSThe patients with TBM diagnosed on the basis of clinical, cerebrospinal fluid (CSF) and MRI criteria were included. Children below 15 years, patients with pregnancy, seizures, liver failure, kidney failure and malignancy were excluded. The baseline clinical, CSF and MRI characteristics were noted and consciousness was evaluated by Glasgow Coma Scale (GCS). The patients were randomized to RHZE (rifampicin, isoniazid, pyrazinamide and ethambutol) and RHZEL (RHZE and levofloxacin) groups. Outcome was defined at 6 months. Primary outcome was death and secondary outcomes were disability as assess by Barthel Index score and adverse events.RESULTSOut of 110 TBM patients screened, 57 fulfilled the inclusion criteria. Their median age was 35 (15-75) years. 29 patients received RHZEL and 28 RHZE. The baseline clinical, biochemical and MRI characteristics were similar in the two groups. At 6 months, 11 (19.3%) patients died, 38 (66.7%) had good and 7 (12.3%) poor outcome. There was insignificant survival benefit in RHZEL group compared to RHZE (HR-2.61, 95% CI 0.73-9.36, P = 0.14), 25% patients died in RHZE where as 13.8% in RHZEL group. The disability was not significantly different between the two groups. The composite side effects were also similar between the two groups except for a higher frequency of seizure in RHZEL group (5 Vs 0) which resulted in withdrawal of levofloxacin.CONCLUSIONThere was insignificant survival benefit in RHZEL which was associated with high frequency of seizures.

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1. **Tuberculous Meningitis in an Immunocompetent Host: A Case Report.**
Khanna Suchin R. The American journal of case reports 2016;17:977-981.

BACKGROUND Tuberculous meningitis is very rare in the United States in immunocompetent hosts. Risk factors are similar to those of pulmonary tuberculosis, including poverty, malnutrition, overcrowding, a compromised immune system, and coming from an endemic area. Meningeal tuberculosis mortality and other outcomes have changed little over time despite effective therapies due to delay in diagnosis because of its rarity, variable presentation, and often indolent course. CASE REPORT We describe a case of a 57-year-old male immigrant from Senegal with no significant past medical history and no previous history of tuberculosis or evidence of immune compromise. He presented to the hospital with headache and altered mental status and was subsequently diagnosed with tuberculous meningitis. CONCLUSIONS This is a rare case of tuberculous meningitis in an immunocompetent host, questioning the conventional view that tuberculous meningitis is a disease of immunocompromised individuals. It emphasizes the importance of maintaining a strong clinical suspicion of tuberculous meningitis even in an immunocompetent patient in a geographical area with low prevalence if the patient has risk factors. Missed or delayed diagnosis is commonly fatal.

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1. **Adding Streptomycin to an Intensified Regimen for Tuberculous Meningitis Improves Survival in HIV-Infected Patients**
Alvarez-Uria G. Interdisciplinary Perspectives on Infectious Diseases 2015;2015:-.

In low- and middle-income countries, the mortality of HIV-Associated tuberculous meningitis (TM) continues to be unacceptably high. In this observational study of 228 HIV-infected patients with TM, we compared the mortality during the first nine months of patients treated with standard antituberculosis therapy (sATT), intensified ATT (iATT), and iATT with streptomycin (iATT + STM). The iATT included levofloxacin, ethionamide, pyrazinamide, and double dosing of rifampicin and isoniazid and was given only during the hospital admission (median 7 days, interquartile range 6-9). No mortality differences were seen in patients receiving the sATT and the iATT. However, patients receiving the iATT + STM had significant lower mortality than those in the sATT group (hazard ratio [HR] 0.47, 95% confidence interval [CI] 0.24 to 0.93). After adjusting for other covariates, the mortality hazard of the iATT + STM versus the sATT remained statistically significant (adjusted HR 0.2, 95% CI 0.09 to 0.46). Other factors associated with mortality were previous ATT and low albumin concentrations. The mortality risk increased exponentially only with CD4+ lymphocyte concentrations below 100 cells/L. In conclusion, the use of iATT resulted in a clinically important reduction in mortality compared with the standard of care only if associated with STM. The results of this study deserve further research.<br/>Copyright &#xa9; 2015 Gerardo Alvarez-Uria et al.

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1. **An unusual presentation of tuberculous meningitis**
Sali S. Archives of Clinical Infectious Diseases 2015;10(3):-.

Introduction: Tuberculosis (TB) is one of the most lethal infectious diseases, responsible for high levels of mortality and morbidity. Tuberculous meningitis (TBM) is one of the most severe presentations of extra-pulmonary tuberculosis. Due to its nonspecific signs and symptoms, diagnosis delay and neurological sequelae are common. Thus, it is important to report rare TBM manifestations. Case Presentation: A 66-year-old diabetic man was admitted to our hospital. He complained of prolonged left otalgia and headache. Antibiotic therapy was started for mastoiditis and otitis media. Since his pain did not subside, glucocorticoid therapy was later prescribed to treat suspected temporal arteritis. However, the patient did not respond to treatment. Additional investigations such as imaging and laboratory data were performed, and the patient was finally diagnosed with TBM. The patient subsequently underwent anti-TB treatment. Conclusions: Clinicians should be aware that TBM might have unusual presentations. Early diagnosis and treatment are essential to decrease mortality and morbidity such as irreversible neurological deficits.<br/>Copyright &#xa9; 2015, Infectious Diseases and Tropical Medicine Research Center.

1. **Pediatric tuberculous meningitis: Model-based approach to determining optimal doses of the anti-tuberculosis drugs rifampin and levofloxacin for children.**
Savic R. M Clinical pharmacology and therapeutics 2015;98(6):622-629.

Pediatric tuberculous meningitis (TBM) is a highly morbid, often fatal disease. Standard treatment includes isoniazid, rifampin, pyrazinamide, and ethambutol. Current rifampin dosing achieves low cerebrospinal fluid (CSF) concentrations, and CSF penetration of ethambutol is poor. In adult trials, higher-dose rifampin and/or a fluoroquinolone reduced mortality and disability. To estimate optimal dosing of rifampin and levofloxacin for children, we compiled plasma and CSF pharmacokinetic (PK) and outcomes data from adult TBM trials plus plasma PK data from children. A population PK/pharmacodynamic (PD) model using adult data defined rifampin target exposures (plasma area under the curve (AUC)0-24 = 92 mg\*h/L). Levofloxacin targets and rifampin pediatric drug disposition information were literature-derived. To attain target rifampin exposures, children require daily doses of at least 30 mg/kg orally or 15 mg/kg intravenously (i.v.). From our pediatric population PK model, oral levofloxacin doses needed to attain exposure targets were 19-33 mg/kg. Our results provide data-driven guidance to maximize pediatric TBM treatment while we await definitive trial results.

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1. **Pharmacokinetic/pharmacodynamic analysis of an intensified regimen containing rifampicin and moxifloxacin for tuberculous meningitis**
Te Brake L. International Journal of Antimicrobial Agents 2015;:-.

Recent data suggest that intensified antimicrobial treatment may improve the outcome of tuberculous meningitis (TBM). Considering that drug exposure is the intermediate link between dose and effect, we examined the concentration-response relationship for rifampicin and moxifloxacin in TBM patients. In an open-label, phase 2 clinical trial performed in Indonesia (ClinicalTrials.gov NCT01158755), 60 TBM patients were randomised to receive standard-dose (450mg oral) or high-dose rifampicin (600mg intravenous) plus either oral moxifloxacin (400mg or 800mg) or ethambutol (750mg). After 14 days, all patients continued with standard tuberculosis treatment. Pharmacokinetic sampling was performed once in every patient during the first three critical days. Differences in exposure between patients who died or survived were tested with independent samples t-tests. The relationship between drug exposure and mortality was examined using Cox regression. Compared with patients who died during the 2 weeks of intensified treatment, surviving patients had significantly higher rifampicin plasma AUC<sub>0-6h</sub>, plasma C <sub>max</sub> and CSF C <sub>highest</sub>. Additionally, patients had a 32-43% lower relative likelihood of dying with an interquartile range increase in rifampicin exposure. Moxifloxacin exposure did not show a clear relationship with survival. From exposure-response curves, a rifampicin plasma AUC<sub>0-6h</sub> of ~70mg.h/L (AUC<sub>0-24h</sub> of ~116mgh/L) and a C <sub>max</sub> of ~22mg/L were deduced as minimum target values for treatment. A strong concentration-effect relationship was found, with higher rifampicin exposure leading to better TBM survival. The current treatment dose of rifampicin is suboptimal; higher doses of rifampicin should be evaluated.<br/>Copyright &#xa9; 2015 Elsevier B.V. and the International Society of Chemotherapy.

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1. **Treatment for tuberculosis in a patient with Dubin-Johnson syndrome.**
Alpana Meena BMJ case reports 2015;2015:-.

Dubin-Johnson syndrome (DJS) is an autosomal recessive disorder characterised by conjugated hyperbilirubinemia resulting from mutations of ABCC2/MRP2 gene. The beneficial effects of ursodeoxycholic acid (UDCA) and rifampicin were found to be complementary in the treatment of cholestatic liver disease secondary to DJS. We present a case of a young woman with tubercular meningitis. She was started on modified antitubercular therapy in view of conjugated hyperbilirubinemia. However, reinitiation of rifampicin resulted in redevelopment of jaundice. Liver biopsy was suggestive of DJS. The patient was started on rifampicin along with UDCA. There was improvement in hyperbilirubinemia and a full course of antituberculous therapy without further worsening of the disorder was possible. This is a rare case of DJS with tuberculosis, showing beneficial effects of rifampicin and UDCA combination therapy, which so far has been considered doubtful. It is uncertain what the level of efficacy of therapy is in various MRP2 gene mutations.

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1. **Tuberculous meningitis: advances in diagnosis and treatment.**
Török M. E British medical bulletin 2015;113(1):117-131.

INTRODUCTIONTuberculous meningitis (TBM) is the most severe form of infection caused by Mycobacterium tuberculosis, causing death or disability in more than half of those affected. The aim of this review is to examine recent advances in our understanding of TBM, focussing on the diagnosis and treatment of this devastating condition.SOURCES OF DATAPapers on TBM published between 1891 and 2014 and indexed in the NCBI Pubmed. The following search terms were used: TBM, diagnosis, treatment and outcome.AREAS OF AGREEMENTThe diagnosis of TBM remains difficult as its presentation is non-specific and may mimic other causes of chronic meningoencephalitis. Rapid recognition of TBM is crucial, however, as delays in initiating treatment are associated with poor outcome. The laboratory diagnosis of TBM is hampered by the low sensitivity of cerebrospinal fluid microscopy and the slow growth of M. tuberculosis in conventional culture systems. The current therapy of TBM is based on the treatment of pulmonary tuberculosis, which may not be ideal. The combination of TBM and HIV infection poses additional management challenges because of the need to treat both infections and the complications associated with them.AREAS OF CONTROVERSYThe pathogenesis of TBM remains incompletely understood limiting the development of interventions to improve outcome. The optimal therapy of TBM has not been established in clinical trials, and increasing antimicrobial resistance threatens successful treatment of this condition. The use of adjunctive anti-inflammatory agents remains controversial, and their mechanism of action remains incompletely understood. The role of surgical intervention is uncertain and may not be available in areas where TBM is common.GROWING POINTSLaboratory methods to improve the rapid diagnosis of TBM are urgently required. Clinical trials of examining the use of high-dose rifampicin and/or fluoroquinolones are likely to report in the near future.AREAS TIMELY FOR DEVELOPING RESEARCHThe use of biomarkers to improve the rapid diagnosis of TBM warrants further investigation. The role of novel antituberculosis drugs, such as bedaquiline and PA-824, in the treatment of TBM remains to be explored. Human genetic polymorphisms may explain the heterogeneity of response to anti-inflammatory therapies and could potentially be used to tailor therapy.

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1. **[A case of tuberculous meningitis complicated with multiple drug hypersensitivity to antituberculosis agents].**
Arai Motomi Rinsho shinkeigaku = Clinical neurology 2015;55(2):123-125.

Multiple drug hypersensitivity (MDH) is an allergy to two or more chemically unrelated drugs. We present a case of MDH caused by antituberculosis agents during the treatment of tuberculous meningitis (TBM). A 64-year-old man without a history of drug allergy developed fever and severe headache. Examination of cerebrospinal fluid showed lymphocytosis, a low glucose level, and a high ADA activity, suggestive of TBM. The patient was treated with isoniazid, rifampicin, pyrazinamide, and ethambutol, and his symptoms resolved quickly. However, 20 days after the initiation of therapy, he developed remittent fever without mucocutaneous lesions. A drug-induced lymphocyte stimulation test was positive for isoniazid, rifampicin, and pyrazinamide, which was consistent with a diagnosis of MDH. All the antituberculosis drugs were replaced with levofloxacin and ethionamide, both of which have excellent cerebrospinal fluid penetration, and the fever subsided. The patient made a full recovery from TBM. Because standard antituberculosis regimens include three or four antituberculosis drugs, it is difficult to determine the culprit drug when hypersensitivity occurs. Moreover, there can be multiple causative drugs as illustrated by the present case. During a time-consuming desensitization therapy, TBM could flare up, leading to permanent neurological damage. Thus, treatment with suitable alternative drugs should be started immediately.

1. **CNS TB with initially negative AFB**
Haftka A.C. Journal of General Internal Medicine 2014;29:-.

LEARNING OBJECTIVE 1: Assess an atypical presentation of CNS tuberculosis. LEARNING OBJECTIVE 2: Diagnosis CNS tuberculosis without systemic findings. CASE: An 82 year-old middle eastern male from Yemen with an extensive past medical history significant for a-fib, diabetes mellitus, cryptogenic cirrhosis, and prostate cancer was initially brought to the emergency room due to altered mental status and acute renal failure. CT scan and MRI revealed multiple ring enhancing lesions located in the left cerebellum and parietal lobe as well as in the right frontal lobe. The initial impression was infectious versus metastatic process as the patient had a recent history of prostate cancer, however, PSA levels were undetectable. The patient was placed on a prophylactic antibiotic regimen that included vancomycin, cefepime, and flagyl and initially had a marginal response with diminishing lesions, decreasing vasogenic edema, and improving mental status. Preliminary testing for infectious causes included an extensive workup including blood cultures, fungitell, PPD skin testing, chest xray and CT, bronchiolar lavage with culture, and Quantiferon TB gold which were all negative. Although the initial follow-up MRI showed a preliminary improvement in the size of the brain lesions, a subsequent MRI 1 month later showed profound worsening of the lesions with increasing vasogenic edema and new found mass effect impinging on the fourth ventricle. The patient's course was further complicated by the development of generalized anasarca attributed to worsening renal versus liver function as well as poor nutritional status. The patient's mental status and overall health continued to decline and additionally developed a-fib with RVR and respiratory distress. Furthermore, the patient was transferred to the intensive care unit with hypoxic respiratory failure due to increasing secretions and inability to protect his airway and was intubated for the remainder of his hospital stay. Therefore, brain biopsy was deferred until the patient stabilized 3 weeks later. The diagnosis of CNS tuberculosis was finally confirmed by drainage of the posterior brain abscesses revealing positive AFB cultures. The following day the patient had a bronchial lavage, which was also AFB positive. The patient was started on standard tuberculosis therapy but unfortunately expired after 8 days of antibiotic treatment due to worsening renal failure and electrolyte abnormalities inducing cardiac arrest. DISCUSSION: Central nervous system tuberculosis is more frequently seen in endemic areas where there is a higher prevalence of tuberculosis. If seen in less prevalent areas, such as the United States, it is thought to be a post-primary result of systemic TB. CNS tuberculosis may present as a tuberculoma, meningitis, or spinal tuberculous arachnoiditis. Based on previous case reports the findings of CNS TB without systemic findings, such as pulmonary involvement, is very rare. Usually patient's will present with seizure as a primary symptom, suggesting our patient had a very atypical presentation. He presented with altered mental status and new onset renal failure. The patient was also negative for AFB, Quantiferon Gold, and PPD. There appeared to be no evidence supporting the diagnosis of TB, especially in the CNS. This makes our case very unusual. For diagnosis purposes CT imaging of the head will show small rings with surrounding edema. As they mature they become larger by coalescing together and becoming lobulated. MRI is thought to be the best imaging study. Biopsy should only be done if the tuberculoma is located in a safe location where there is a decreased chance of causing any injury to the brain. There is mixed views, based on several studies, as to whether biopsy is the best approach to diagnosis. Treatment should always be started when there is a high clinical suspicion for TB for a better clinical outcome. First line therapy includes INH, Rifampin, Ethambutol, Streptomycin, and Pyrazinamide. For the first 2 months of therapy the patient should receive 4 agents (INH, Rifampin, Ethambutol and Streptomycin or Pyrazinamide). After this 2 month period, a patient should remain on therapy for additional 7-10 months of Rifampin or INH. Our patient was immediately started on the intense regimen of INH, Rifampin, Ethambutol, and Pyrazinamide, but unfortunately due to the late diagnosis of CNS TB, our patient was unable to benefit from treatment.

1. **High dose versus low dose steroids in children with tuberculous meningitis**
Shah I. Journal of Clinical Neuroscience 2014;21(5):761-764.

Guidelines for the best steroid dose in children with tuberculous meningitis (TBM) have not been established. We enrolled 63 children with TBM and divided them into three steroid dose groups: Group 1 (prednisolone 2 mg/kg/day over 4 weeks), Group 2 (prednisolone 4 mg/kg/day over 1 week and 2 mg/kg/day for the next 3 weeks) and Group 3 (prednisolone 4 mg/kg/day over 4 weeks). All patients received standard antituberculous therapy. Optic atrophy, tuberculoma, hydrocephalus, mental retardation, spasticity, hearing impairment, vasculitis and mortality outcomes were compared. Optic atrophy was higher in Group 3 compared to Group 1 (odds ratio [OR] = 2.8) and Group 2 (OR = 2.8), although Group 3 had a high incidence of optic atrophy at diagnosis. Tuberculomas were more frequent in Group 1 (OR = 2.4) and Group 3 (OR = 3.0) as compared to Group 2. Infarcts were more common in Group 3 than in Group 1 (OR = 1.9) and in Group 2 (OR = 3.5). Hearing loss was higher in Group 2 as compared to Group 1 (OR = 2.88) and Group 3 (OR = 4.8). Evolving hydrocephalus was higher in Group 3 as compared to Group 2 (OR = 2.8) and Group 1 (OR = 3.1). Mental retardation was higher in children in Group 3 (OR = 1.6) and in Group 2 (OR = 1.9) as compared to Group 1. Spasticity was higher in Group 3 (OR = 2.0) and in Group 2 (OR = 1.4) as compared to Group 1. There was no difference in mortality between the groups. We conclude that prednisolone at a dose of 4 mg/kg/day for 1 week followed by 2 mg/kg/day for 3 weeks is associated with fewer tuberculomas and infarcts but a higher incidence of hearing loss. A prolonged period of high dose steroids increases the risk of optic atrophy and hydrocephalus. Prednisolone at a dose of 2 mg/kg/day is associated with lower risk of mental retardation and spasticity. &#xa9; 2013 Elsevier Ltd. All rights reserved.

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1. **In reply: short intensified treatment in children with drug-susceptible tuberculous meningitis.**
van Toorn Ronald The Pediatric infectious disease journal 2014;33(9):993-994.

1. **Management of paradoxical response in pediatric tubercular meningitis with methylprednisolone.**
Nema Nitin Middle East African journal of ophthalmology 2014;21(2):189-192.

Paradoxical response to anti-tubercular drugs remains a diagnostic dilemma. In India where tuberculosis is quite prevalent, paradoxical response to anti-tubercular treatment (ATT) is either misdiagnosed or under-diagnosed. We report two cases of optochiasmatic arachnoiditis due to paradoxical response in children suffering from tuberculous meningitis. Visual acuity was recorded as no light perception in all eyes of both patients while they were taking 4-drug ATT (isoniazid, rifampicin, pyrazinamide and ethambutol). However their systemic conditions did not worsen. They were treated with intravenous methylprednisolone for five days followed by systemic corticosteroids on a tapering dose for four weeks along with ATT. This case report highlights the importance of early recognition of this sight-threatening complication and timely, effective treatment to prevent permanent blindness.

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1. **Resolution of tubercular abscess with antitubercular treatment.**
Sarangi G. S The Indian journal of tuberculosis 2014;61(4):336-339.

Tubercular brain abscess is a rare manifestation of neurotuberculosis. Large brain absceses are usually surgically treated. We report a case of tubercular brain abscesses in left cerebellar hemisphere and right parietal lobe in a child who was treated surgically for the cerebellar abscess and conservatively with antitubercular drug for parietal abscess. The patient showed significant clinical improvement and healing of brain abscess on follow up imaging. The resolution of relatively large abscess by conservative management with antitubercular treatment is very rare.

1. **Safety and efficacy of levofloxacin versus rifampicin in tuberculous meningitis: an open-label randomized controlled trial.**
Kalita J. The Journal of antimicrobial chemotherapy 2014;69(8):2246-2251.

OBJECTIVESWe report the efficacy and safety of levofloxacin versus rifampicin in tuberculous meningitis (TBM).PATIENTS AND METHODSIn this open-label, randomized controlled trial from India, patients with TBM diagnosed on the basis of clinical, MRI and CSF findings were included. Patients with hepatic or renal dysfunction, organ transplantation, malignancy, pregnancy, lactation, allergy, seizure, age <15 years and antitubercular treatment ≥1 month were excluded. Sixty patients each were randomized to levofloxacin (10 mg/kg, maximum 500 mg) or rifampicin (10 mg/kg, maximum 450 mg). They also received isoniazid, pyrazinamide, ethambutol, prednisolone and aspirin. The primary outcome was death and secondary outcome measures were 6 month disability, repeat MRI changes and serious adverse events (SAEs).RESULTSThe median age of the patients was 34.5 (16-75) years. The baseline clinical and MRI findings were similar between the two groups. At 6 months, 13 out of 60 (21.7%) patients in the levofloxacin arm and 23 out of 60 (38.3%) patients in the rifampicin arm had died (P = 0.07). On Cox regression analysis, survival in the levofloxacin group was significantly better than in the rifampicin group (hazard ratio 2.13, 95% CI 1.04-4.34, P = 0.04). The functional outcome (P = 0.47) was, however, not significantly different between the two groups. On intention-to-treat analysis, 10 out of 47 (21.3%) in the levofloxacin arm and 5 out of 37 (13.5%) in the rifampicin arm had poor recovery. Repeat MRI findings did not differ between the groups. Levofloxacin was discontinued more frequently than rifampicin due to SAEs (16 versus 4, P = 0.01).CONCLUSIONSLevofloxacin is superior to rifampicin in reducing 6 month death in TBM but not disability. Levofloxacin may be used in TBM especially in those patients with hepatotoxicity and without seizure.

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1. **Short intensified treatment in children with drug-susceptible tuberculous meningitis.**
van Toorn Ronald The Pediatric infectious disease journal 2014;33(3):248-252.

BACKGROUNDThe World Health Organization recommends 12-month treatment (2RHZE/10RH) for children with tuberculous meningitis (TBM). Studies evaluating length of antituberculous treatment for TBM report similar completion and relapse rates comparing 6-month treatment with 12-month treatment.METHODSA prospective evaluation to determine whether short-course intensified treatment (6 RHZEth for HIV-infected and 9RHZEth for HIV-infected) is sufficient and safe in children with drug-susceptible TBM.RESULTSOf 184 children with TBM, median age 58 months and 90 (49%) male, 98 children (53%) presented at stage II TBM, 64 (35%) at stage III TBM and only 22 (12%) at stage I TBM. Ninety (49%) children were treated at home after the first month of therapy; all others received their full treatment in hospital. The HIV prevalence was 14% (22/155 children tested). Anti-TB drug-induced hepatotoxicity occurred in 5% (8 of 143 children tested), all tested negative for viral hepatitis; in all 8 cases, the original regimen was restarted without recurrence. After treatment completion, 147 (80%) children had a good outcome, 7 (3.8%) died. There was no difference in outcome between HIV-infected and HIV-uninfected children who completed treatment (P = 0.986) nor between TBM-hydrocephalic children who were medically treated or shunted (P = 0.166).CONCLUSIONShort intensified treatment is safe and effective in both HIV-infected and HIV-uninfected children with drug-susceptible TBM.

1. **Tuberculoma masked by glioma: A case report**
Sun X.-F. Genetics and Molecular Research 2014;13(4):10450-10453.

Tuberculous meningitis (TM), a common infectious disease of the central nervous system that is also seen in other types of tuberculosis infections, has higher mortality rates in young and middle-aged patients. TM is difficult to diagnose and treat owing to its non-specific clinical features and often atypical cerebrospinal fluid changes. Patients who present with focal neurologic signs, cough, low-grade fever and illness duration of more than 5 days, have intracalvarial abnormalities, and do not meet Thwaites' criterion findings should be diagnosed using computed tomography or magnetic resonance imaging. Mycobacterium infections can also be diagnosed by acid-fast staining of smears, cerebrospinal fluid culture, diagnostic polymerase chain reaction for Mycobacterium tuberculosis, and purified protein derivative test. To prevent TM misdiagnosis, clinicians must have sufficient knowledge of the clinical manifestations of tuberculosis. Appropriate application of tuberculosis chemotherapy drug principles, including early diagnosis and treatment, combination therapies, and consistent administration of treatment at appropriate dosages, can greatly reduce TM mortality rates and improve satisfactory treatment outcomes.<br/>Copyright &#xa9; FUNPEC-RP.

1. **Disseminated cerebral and spinal tuberculomas: rare cause of triparesis.**
Verma Rajesh BMJ case reports 2013;2013:-.

Tuberculosis continues to remain a significant public health problem in developing nations, causing substantial morbidity and mortality. Central nervous system (CNS) tuberculosis is frequently observed in endemic zones of tuberculosis including India. The emergence of infections like HIV and malnutrition ruined the public health measures to restrain tuberculosis in developing countries. The incidence of intraspinal tuberculomas is reported to be 0.2-5% among CNS tuberculomas. To date, only a few cases have been reported of mixed intraspinal and intracranial tuberculomas. The clinical outcome in CNS disseminated tuberculomas is not well described in the literature. With this view, we report a case of a 25-year-old woman who presented with neck pain, triparesis and bladder incontinence, which finally proved to be a case of multiple cerebral and spinal tuberculomas. The antitubercular treatment with steroids and other supportive measures resulted in good recovery.

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1. **Intensified intravenous rifampicin in tuberculous meningitis.**
Brouwer Matthijs C. The Lancet. Infectious diseases 2013;13(1):2-3.

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1. **Intensified regimen containing rifampicin and moxifloxacin for tuberculous meningitis: An open-label, randomised controlled phase 2 trial**
Ruslami R. The Lancet Infectious Diseases 2013;13(1):27-35.

Background: Intensified antibiotic treatment might improve the outcome of tuberculous meningitis. We assessed pharmacokinetics, safety, and survival benefit of several treatment regimens containing high-dose rifampicin and moxifloxacin in patients with tuberculous meningitis in a hospital setting. Methods: In an open-label, phase 2 trial with a factorial design in one hospital in Indonesia, patients (aged &gt;14 years) with tuberculous meningitis were randomly assigned to receive, according to a computer-generated schedule, first rifampicin standard dose (450 mg, about 10 mg/kg) orally or high dose (600 mg, about 13 mg/kg) intravenously, and second oral moxifloxacin 400 mg, moxifloxacin 800 mg, or ethambutol 750 mg once daily. All patients were given standard-dose isoniazid, pyrazinamide, and adjunctive corticosteroids. After 14 days of treatment all patients continued with standard treatment for tuberculosis. Endpoints included pharmacokinetic analyses of the blood and cerebrospinal fluid, adverse events attributable to tuberculosis treatment, and survival. Analysis was by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT01158755. Findings: 60 patients were randomly assigned to receive rifampicin standard dose (12 no moxifloxacin, ten moxifloxacin 400 mg, and nine moxifloxacin 800 mg) and high dose (ten no moxifloxacin, nine moxifloxacin 400 mg, and ten moxifloxacin 800 mg). A 33% higher dose of rifampicin, intravenously, led to a three times higher geometric mean area under the time-concentration curve up to 6 h after dose (AUC<sub>0-6</sub>; 78.7 mg.h/L [95% CI 71.0-87.3] vs 26.0 mg.h/L [19.0-35.6]), maximum plasma concentrations (C<sub>max</sub>; 22.1 mg/L [19.9-24.6] vs 6.3 mg/L [4.9-8.3]), and concentrations in cerebrospinal fluid (0.60 mg/L [0.46-0.78] vs 0.21 mg/L [0.16-0.27]). Doubling the dose of moxifloxacin resulted in a proportional increase in plasma AUC<sub>0-6</sub> (31.5 mg.h/L [24.1-41.1] vs 15.1 mg.h/L [12.8-17.7]), C<sub>max</sub> (7.4 mg/L [5.6-9.6] vs 3.9 mg/L [3.2-4.8]), and drug concentrations in the cerebrospinal fluid (2.43 mg/L [1.81-3.27] vs 1.52 mg/L [1.28-1.82]). Intensified treatment did not result in increased toxicity. 6 month mortality was substantially lower in patients given high-dose rifampicin intravenously (ten [35%] vs 20 [65%]), which could not be explained by HIV status or severity of disease at the time of presentation (adjusted HR 0.42; 95% CI 0.20-0.91; p=0.03). Interpretation: These data suggest that treatment containing a higher dose of rifampicin and standard-dose or high-dose moxifloxacin during the first 2 weeks is safe in patients with tuberculous meningitis, and that high-dose intravenous rifampicin could be associated with a survival benefit in patients with severe disease. Funding: Royal Dutch Academy of Arts and Sciences, Netherlands Foundation for Scientific Research, and Padjadjaran University, Bandung, Indonesia. &#xa9; 2013 Elsevier Ltd.

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1. **Isoniazid- and streptomycin-resistant miliary tuberculosis complicated by intracranial tuberculoma in a Japanese infant.**
Ishiwada Naruhiko The Tohoku journal of experimental medicine 2013;229(3):221-225.

In Japan, the incidence of severe pediatric tuberculosis (TB) has decreased dramatically in recent years. However, children in Japan can still have considerable opportunities to contract TB infection from adult TB patients living nearby, and infants infected with TB may develop severe disseminated disease. A 3-month-old girl was admitted to our hospital with dyspnea and poor feeding. After admission, miliary TB and multiple brain tuberculomas were diagnosed. Anti-tuberculous therapy was initiated with streptomycin (SM), isoniazid (INH), rifampicin and pyrazinamide. Symptoms persisted after starting the initial treatment and mycobacterial cultures of gastric fluid remained positive. Drug sensitivity testing revealed the TB strain isolated on admission as completely resistant to INH and SM. Treatments with INH and SM were therefore stopped, and treatment with ethambutol and ethionamide was started in addition to rifampicin and pyrazinamide. After this change to the treatment regimen, symptoms and laboratory data gradually improved. The patient was treated with these four drugs for 18 months, and then pyrazinamide was stopped. After another 2 months, ethambutol was stopped. Treatment of tuberculosis was completed in 24 months. No adverse effects of these anti-TB drugs were observed. The patient achieved a full recovery without any sequelae. On the other hand, the infectious source for this patient remained unidentified, despite the extensive contact investigations. The incidence of drug-resistant TB is increasing in many areas of the world. Continuous monitoring for pediatric patients with drug-resistant TB is therefore needed.

1. **Phenytoin-rifampin drug interaction in a hypoalbuminemic, renal failure patient: a complex clinical case.**
Van Berkel Megan A. Pharmacotherapy 2013;33(6):e96-.

Phenytoin, a commonly used antiepileptic, is difficult to dose optimally due to its narrow therapeutic window, nonlinear pharmacokinetics, extensive protein binding, and participation in clinically significant drug interactions. Although clinicians are aware of the interaction with two widely used antituberculosis agents, rifampin and isoniazid, few reports have described the implications for managing phenytoin dosing in this situation. To our knowledge, only two reports of the clinical experience with this interaction have been published, and only one of these reports involved the addition of isoniazid. We present a case of a 60-year-old man treated with triple antiepileptic therapy, including phenytoin, who experienced seizures shortly after hospital admission. Dosing of phenytoin proved difficult in this patient due to an acute kidney injury and severe hypoalbuminemia requiring hemodialysis. A further complexity was the addition of antituberculosis therapy (rifampin, isoniazid, pyrazinamide, and ethambutol [RIPE]) for suspected tuberculosis meningitis after the patient experienced persistent encephalopathy. Phenytoin concentrations decreased steadily after rifampin and isoniazid initiation despite dose increases, and the free concentration of phenytoin reached a low of less than 0.5 µg/ml on day 8 of RIPE therapy. The patient continued on a stable dose of phenytoin and RIPE therapy for unconfirmed tuberculosis meningitis until discharge. This report is the first description of this drug interaction in 20 years and highlights the need for appropriate management of phenytoin in a patient with complicated needs for pharmacotherapy.

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1. **Severe hyponatremia and MRI point to diagnosis of tuberculous meningitis in the Southwest USA.**
Benson Stephanie Michelle BMJ case reports 2013;2013:-.

A 21-year-old woman presented to the hospital with 3 days of headache, fever, mood disturbance and nausea. She had recently emigrated from India, and was noted to have a positive screening purified protein derivative tuberculosis skin test with normal chest x-ray. Meningeal signs were noted prompting lumbar puncture and initiation of presumptive treatment for bacterial meningitis. While tuberculous meningitis (TM) was entertained at admission, diagnosis was clouded by the rapid onset of symptoms and recent major psychosocial stressors. She developed severe hyponatremia. Brain MRI revealed tuberculomas, and she was started on treatment for TM, a diagnosis confirmed by culture. On review, several lessons were learned: (1) globalisation of society makes uncommon diagnoses present in unlikely locations, (2) hyponatremia is a common complication of TM, (3) MRI can aid in diagnosis of TM and (4) cognitive and mood changes can be prodromal symptoms of TM.

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1. **Tuberculous meningitis--a case report.**
Guziejko Katarzyna Przeglad epidemiologiczny 2013;67(4):629-.

In this paper we present a case of a 58 years old male with a rare form of extrapulmonary tuberculosis--tuberculous meningitis (TBM). Tuberculous meningitis is usually caused by hematogenous spread of Mycobacterium from lungs. The TBM is a severe disease with high mortality. The symptoms usually increase gradually and in the course of the disease 3 clinical stages (prodromal phase, phase of neurological symptoms and phase of paresis) may be differentiated. Cerebrospinal fluid examination, chest x-ray and sputum culture are crucial for diagnosis of TBM. The proper diagnosis and early causative treatment significantly improve the outcome of the disease.

1. **Unfinished battle with childhood tuberculosis: is it curable with less drugs and shorter duration?**
Cinel G.üzin Tuberkuloz ve toraks 2013;61(4):320-326.

INTRODUCTIONTuberculosis is still a global health problem all over the world despite its mortality has been decreased with effective treatment regimens. Poor treatment adherence, acquired drug resistance, treatment failure and relapse are the major problems during the course of the tuberculosis treatment. Intermittent regimens have the advantages of reducing the side effects and the cost of the therapy and increasing the adherence, especially in resource-limited areas; and have been documented to be as effective as daily regimen in the paediatric population. In this study, we compared the results of 6-month and 9-month intermittent-therapy regimens with two drugs, given to the children with pulmonary and extrapulmonary tuberculosis at our hospital.MATERIALS AND METHODSOne hundred and fifteen patients with pulmonary and extrapulmonary tuberculosis other than meningitis, who had been given intermittent anti-tuberculosis therapy between 1986 and 2001, were evaluated retrospectively. Fifty one patients were given isoniazid and rifampin daily for 15 days, followed by the same drugs and doses twice weekly for a total of 9-months. Also, 64 patients were treated with the same regimen for a total of 6-months.RESULTSClinical recovery was observed in 75% and 79% of pulmonary tuberculosis patients at the first month of therapy in group 1 (9-month group) and group 2 (6-month group), respectively. Radiological recovery was noted between 0-6 months in 81% of the patients in group 1 and 86% of the patients in group 2. According to the clinical and radiological recovery times, no significant difference was detected between the two groups (p> 0.05). Similar results had been observed in extrapulmonary tuberculosis (p> 0.05). Follow-up periods ranged from 7 months to 15 years. There was no case of early relapse. Late relapse was noted in 4 patients, who had been received 9-month therapy (group 1).CONCLUSIONSix-month intermittent therapy with two drugs is as efficacious as 9-month intermittent-therapy in childhood pulmonary and extrapulmonary tuberculosis, other than meningitis.

1. **[Papilledema secondary to tuberculous meningitis in a patient with type 1 diabetes mellitus].**
Caire Estévez J. P Archivos de la Sociedad Espanola de Oftalmologia 2013;88(10):403-406.

CASE REPORTThe case is presented of a 29-year-old woman who complained of headache over a period of several days, with loss of visual acuity and pain in her left eye. She had a 3-year history of type 1 diabetes mellitus, and was an immigrant from Ecuador. The funduscopic examination revealed a papilledema. The polymerase chain reaction (PCR) study of the cerebrospinal fluid was positive for Mycobacterium tuberculosis (MTB). She showed a marked improvement after treatment with anti-TB drugs.DISCUSSIONAbout a third of the world's population has a latent infection of MTB, comorbidity between diabetes mellitus and tuberculosis has been reported, particularly in undeveloped countries.

1. **Anhelation due to formation of tuberculomas at the medulla oblongata during chemotherapy of tuberculous meningitis.**
Ge Pengfei Neurologia i neurochirurgia polska 2012;46(5):501-505.

Formation of tuberculoma is a rare response of neurotuberculosis in patients regularly and adequately treated with anti-tuberculous drugs. We report a 13-year-old girl with two tuberculomas which formed in the dorsal part of the medulla oblongata during chemotherapy for tuberculous meningitis. The tuberculomas were both removed via a suboccipital midline approach and were demonstrated by pathological findings but the girl died of cardiac arrest that was thought to be caused by postoperative medulla oblongata oedema. In combination with a literature review, we discuss the clinical features and treatment options of brainstem tuberculomas.

1. **Management of tuberculosis in HIV-infected patients**
Curran A. AIDS Reviews 2012;14(4):231-246.

HIV-tuberculosis coinfection is currently one of the greatest health threats, affecting millions of people worldwide, with high morbidity and mortality. Treating both infections can be a challenge and requires some expertise due to multidirectional drug interactions, risk of overlapping side effects, high pill burden and risk of immune reconstitution inflammatory syndrome. This article reviews the general management of tuberculosis/HIV coinfection, focusing on the optimal time to start antiretroviral therapy and which treatments can be safely used. The randomized clinical trials designed to answer the question of when to start antiretroviral therapy (SAPIT, CAMELIA, STRIDE and TIME), published in the last two years, are described and discussed in detail. Summarizing these trials' conclusions, antiretroviral therapy should be started within two weeks of starting tuberculosis treatment if the patient has less than 50 CD4/mm<sup>3</sup> and wait to the end of the induction phase (8-12 weeks after starting tuberculosis treatment) if higher CD4 cell counts exist. Treatment options for both tuberculosis and HIV, including the newer available drugs and those in clinical trials, are revised and recommendations for dose adjustments are made based on the latest available literature, with special attention to drug-drug interactions and the necessity of dose adjustments with some drug combinations.

1. **Neuroborreliosis as a chameleon-mimicking tuberculous meningitis**
Merfort J. Neuropediatrics 2012;43(2):-.

Aims: Differential diagnosis of a neuroborreliosis Methods: The case of a 16 year old boy with a severe manifestation of a neuroborreliosis is presented. In the initial exploration he appeared with for five weeks increasing spastic-atactic gait abnormality, disturbance of micturition, back pain, hyperactive reflexes with broadened reflex areas, especially regarding the lower limb, with positive Babinski signs and finally inexhaustible cloni. Results: The performed MRI showed leptomeningeal enhancement along the whole spinal cord, transverse myelitis on the level of T 6-8 and polyradiculopathy. In the lumbar punction the cell count was 348/mul with 294 lymphocytes, protein 8.4g/l, glucose 21mg/dl, lactate 5 mM with a massive barrier disturbance. With suspicion of a spinal tuberculosis a tuberculostatic combination therapy according to the appropriate guidelines was initiated and augmented by ceftriaxone to cover a potential neuroborreliosis. The initial serology of the cerebrospinal fluid showed marginal elevated IgM- with distinctly raised IgG-titre. However, due to the massive barrier disturbance an autochthonal antibody production could not be verified. Tbc PCR, direct preparations, skin tests and quantiferon-assay remained negative. With reconstitution of the blood-brain barrier a CSF/serum index appeared for B. burgdorferi-IgM of 9 and for B. b.-IgG of 10. Thereupon, neuroborreliosis phase II/III could be diagnosed. During the three-week intravenous antibiotic therapy the liquor status improved and a nearly complete resolution of the spinal and radicular contrast medium enhancement appeared. Clinically, the gait abnormality improved only to a very small extent, whereas the disturbance of micturition disappeared subjectively. Conclusion: In the presented case of neuroborreliosis an autochthonal borrelia antibody production could only be proved in the course of a normalisation of the blood-brain barrier and therefore resulted in the correct diagnosis finding. The time-consuming exclusion of a tuberculosis necessitated a therapy ex juvantibus.

1. **Pharmacokinetics, safety and effectiveness of high-dose rifampicin and moxifloxacin for tuberculosis meningitis: A randomised clinical trial in Indonesia**
Van Crevel R. Clinical Microbiology and Infection 2012;18:33-34.

Objectives: Tuberculosis meningitis (TBM) has a case fatality rate of &gt;30%. Optimal treatment for TBM has not been established and follows the model of pulmonary TB treatment. Moxifloxacin, because of its potencyand good penetration into the cerebrospinal fluid (CSF) is a promising drug for TBM. Higher doses of moxifloxacin as well as rifampicin may increase drug exposure in blood and CSF, thereby improving survival. This study evaluates the pharmacokinetics (PK), safety and efficacy of such an intensified regimen for TBM in a hospital in Indonesia. Methods: We randomized 60 Indonesian TBM patients (10% HIVinfected) to standard dose (450 mg, 10 mg/kg) oral rifampicin or high dose (600 mg, 13 mg/kg) rifampicin administered i.v., and (in a second randomization) to moxifloxacin 400 mg, moxifloxacin 800 mg, or ethambutol 750 mg QD, for the first 14 days and in adjunction to standard INH, PZA and dexamethason. After the first two weeks of treatment all patients continued with standard TB treatment. Pharmacokinetic (PK) assessments were performed in blood and CSF within the first critical 4 days of treatment, adverse events attributable to TB treatment were assessed, and 1 month mortality was evaluated. This explorative study was powered to detect pharmacokinetic differences between groups. Results: So far PK data have been evaluated for 23 patients. Increasing the dose led to higher drug exposure in plasma for rifampicin (1.8 fold) and moxifloxacin (3-fold). Mean CSF concentrations for rifampicin were low and showed only a small increase with a higher dose (0.50 vs. 0.37 mg/L). Mean CSF concentrations for moxifloxacin were 1.7 vs. 3.9 mg/L (p &lt; 0.05) for standard vs. high dose moxifloxacin. Among the first 48 patients included, mild QTc prolongation occurred in 48% of patients taking moxifloxacin, while grade 3 (10%) and grade 4 (6%) hepatotoxicity was evenly distributed between groups. One-month mortality among the first 48 patients included, was substantially lower (31% vs. 57%, p = 0.07) in patients taking high-dose rifampicin i.v. compared to those taking standard dose orally. Conclusion: Intensified antibiotic treatment for TBM leads to more favorable PK in plasma (rifampicin and moxifloxacin) and in CSF (moxifloxacin), with acceptable toxicity. Preliminary data in this explorative study show a trend for lower mortality in patients taking high dose rifampicin. Larger studies should evaluate the effect of intensified treatment on survival of patients with TBM.

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1. **Tuberculosis in childhood**
Shingadia D. Therapeutic Advances in Respiratory Disease 2012;6(3):161-171.

There has been a recent global resurgence of tuberculosis (TB) fuelled by HIV infection and migration. Childhood TB represents a sentinel event in the community, suggesting recent transmission from an infectious adult. The diagnosis of TB in children is based on chest X-ray, tuberculin skin testing and mycobacterial staining/culture, although the diagnostic yield from these investigations is often lower than in adults. Newer diagnostic tests are being developed and may improve the diagnostic yield in childhood TB. Treatment of TB in children is similar to adults in that short-course multidrug treatment has been adopted as standard therapy in many national TB programmes. Compliance is a major determinant of the success of drug treatment and directly observed therapy has been adopted as a key component of TB treatment programmes. Although uncommon in children, multidrug-resistant TB is also increasing and treatment often involves longer courses of therapy with second-line drugs. &#xa9; The Author(s), 2012.

1. **[Treatment of intractable tuberculous meningitis using intrathecal isoniazid administration and steroid pulse therapy; a report of two cases].**
Takahashi Ikuko Rinsho shinkeigaku = Clinical neurology 2012;52(8):551-556.

Tuberculous meningitis (TbM) is a neurological emergency condition that requires prompt initiation of treatment. The standard initial treatment for TbM is often insufficient for producing remission because the anti-tuberculosis agent may cause severe side effects, or vasculitis and hydrocephalus may induce an intractable state. Moreover, it is difficult to distinguish paradoxical expansion from its own deterioration. We treated 2 cases of adult TbM by using multidisciplinary therapy, including methyl prednisolone pulse and intrathecal isoniazid administration. Both cases had not been diagnosed as pulmonary or other tuberculosis, and cerebrospinal fluid (CSF) culture and polymerase chain reaction at approximately 1 week after hospitalization identified the cases as TbM. We administered the standard initial treatment recommended by the British Infection Society guidelines for adults, but both cases deteriorated and showed elevation of intracranial pressure. We indwelled a lumbar drainage for Case 1 and an Ommaya reservoir for Case 2. We removed CSF and administrated isoniazid regularly using each of the drainage devices, added streptomycin, and increased the steroid dose including addition of steroid pulse therapy. Both cases improved, and their neurological dysfunction did not persist. After the induction of an intractable state occurs due to TbM, we are likely to assume poor prognosis and neurological sequelae. However, our experience in these cases showed amelioration of the symptoms leading to the rehabilitation of these patients in society.

1. **Effectiveness and safety of the schedules of short and long term treatment for tuberculous meningoencephalitis at two hospitals of Lima--Peru.**
Morales S. Neurologia (Barcelona, Spain) 2011;26(4):220-226.

INTRODUCTIONTo compare the effectiveness and safety of short term 6 month-treatment and long term 12 month-treatment schedules for meningoencephalitis due to tuberculosis in two hospitals from Lima-Peru.METHODSComparative, retrospective and observational study. The patients were divided in two groups: Group 1: long term 12 month-treatment with isoniazid, rifampin, pyrazinamide, and ethambutol for the first 2 months; then isoniazid and rifampin for 10 months. Group 2: short term 6 month-treatment with isoniazid and rifampin, pyrazinamide and ethambutol for the first 2 months; then isoniazid and rifampin for 4 months. Clinical records, effectiveness, treatment failure, treatment side effects, mortality and late consequences after treatment were reviewed.RESULTSTwenty-six patients with meningoencephalitis level I were included, 10 received the long term schedule and 16 the short term schedule treatment. From 51 patients with meningoencephalitis level II, 27 received the long term schedule and 24 the short term schedule treatment and of 31 patients with meningoencephalitis level III, 18 received the long term schedule treatment and 13 the short term schedule treatment. There was no statistically significant differences among levels I, II and III when effectiveness of short and long term schedule was evaluated. Moreover, there was no statistically significant difference in the frequency of treatment failure, treatment side effects, mortality and late consequences among groups.CONCLUSIONSLong term 12 month-treatment and short term 6 month-treatment had similar effectiveness and safety in the treatment of meningoenchephalitis due to tuberculosis in HIV negative patients.

1. **Intensified treatment with high dose rifampicin and levofloxacin compared to standard treatment for adult patients with tuberculous meningitis (TBM-IT): protocol for a randomized controlled trial.**
Heemskerk Dorothee Trials 2011;12:25-.

BACKGROUNDTuberculous meningitis is the most severe form of tuberculosis. Mortality for untreated tuberculous meningitis is 100%. Despite the introduction of antibiotic treatment for tuberculosis the mortality rate for tuberculous meningitis remains high; approximately 25% for HIV-negative and 67% for HIV positive patients with most deaths occurring within one month of starting therapy. The high mortality rate in tuberculous meningitis reflects the severity of the condition but also the poor antibacterial activity of current treatment regimes and relatively poor penetration of these drugs into the central nervous system. Improving the antitubercular activity in the central nervous system of current therapy may help improve outcomes. Increasing the dose of rifampicin, a key drug with known poor cerebrospinal fluid penetration may lead to higher drug levels at the site of infection and may improve survival. Of the second generation fluoroquinolones, levofloxacin may have the optimal pharmacological features including cerebrospinal fluid penetration, with a ratio of Area Under the Curve (AUC) in cerebrospinal fluid to AUC in plasma of >75% and strong bactericidal activity against Mycobacterium tuberculosis. We propose a randomized controlled trial to assess the efficacy of an intensified anti-tubercular treatment regimen in tuberculous meningitis patients, comparing current standard tuberculous meningitis treatment regimens with standard treatment intensified with high-dose rifampicin and additional levofloxacin.METHODS/DESIGNA randomized, double blind, placebo-controlled trial with two parallel arms, comparing standard Vietnamese national guideline treatment for tuberculous meningitis with standard treatment plus an increased dose of rifampicin (to 15 mg/kg/day total) and additional levofloxacin. The study will include 750 patients (375 per treatment group) including a minimum of 350 HIV-positive patients. The calculation assumes an overall mortality of 40% vs. 30% in the two arms, respectively (corresponding to a target hazard ratio of 0.7), a power of 80% and a two-sided significance level of 5%. Randomization ratio is 1:1. The primary endpoint is overall survival, i.e. time from randomization to death during a follow-up period of 9 months. Secondary endpoints are: neurological disability at 9 months, time to new neurological event or death, time to new or recurrent AIDS-defining illness or death (in HIV-positive patients only), severe adverse events, and rate of treatment interruption for adverse events.DISCUSSIONCurrently very few options are available for the treatment of TBM and the mortality rate remains unacceptably high with severe disabilities seen in many of the survivors. This trial is based on the hypothesis that current anti-mycobacterial treatment schedules for TBM are not potent enough and that outcomes will be improved by increasing the CSF penetrating power of this regimen by optimising dosage and using additional drugs with better CSF penetration.TRIAL REGISTRATIONInternational Standard Randomised Controlled Trial Number ISRCTN61649292.

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1. **Life-threatening disseminated tuberculosis as a complication of TNF-alpha blockade in an adolescent**
Hess S. European Journal of Pediatrics 2011;170(10):1337-1342.

Life-threatening disseminated tuberculosis developed in a 17-year-old girl who was treated with the TNF-alpha blocker adalimumab for refractory SAPHO syndrome. The patient presented to the emergency department with dyspnea and somnolence and within 2 h developed the clinical picture of a septic shock. In addition to this unusual presentation, she showed a complicated course with increasing cerebral granuloma formation in spite of adequate antimycobacterial treatment. Immune reconstitution after discontinuation of TNF blockade may contribute to this "paradoxical reaction." Possible implications for screening, diagnosis, and treatment of tuberculosis in children and adolescents receiving anti-TNF treatment are discussed. &#xa9; 2011 Springer-Verlag.

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1. **Meningoencephalitis with Aspergillus and mycobacterium tuberculosis in a renal transplant recipient.**
Petramfar Peyman Experimental and clinical transplantation : official journal of the Middle East Society for Organ Transplantation 2011;9(1):68-71.

OBJECTIVESWe report a case of central nervous system coinfection with 2 types of opportunistic organisms-Aspergillus and Mycobacterium tuberculosis-in a 33-year-old woman who underwent a renal transplant.MATERIALS AND METHODSShe developed a high-grade fever and right-sided weakness 1 month after the transplant while on mycophenolate mofetil, prednisolone, and cyclosporine.RESULTSBrain magnetic resonance imaging revealed multiple mass lesions with peripheral ring enhancement. Colony-stimulating factor polymerase chain reaction was positive for Aspergillus and Mycobacterium tuberculosis.CONCLUSIONSBroad-spectrum antibiotics, antituberculous agents, and amphotericin were started. Unfortunately, the woman's condition deteriorated, and she died 2 weeks after admission to the hospital.

1. **Presentation and outcome of tuberculous meningitis in a high HIV prevalence setting**
Marais S. PLoS ONE 2011;6(5):-.

Background: Mycobacterium tuberculosis is a common, devastating cause of meningitis in HIV-infected persons. Due to international rollout programs, access to antiretroviral therapy (ART) is increasing globally. Starting patients with HIV-associated tuberculous meningitis (TBM) on ART during tuberculosis (TB) treatment may increase survival in these patients. We undertook this study to describe causes of meningitis at a secondary-level hospital in a high HIV/TB co-infection setting and to determine predictors of mortality in patients with TBM. Methods: A retrospective review of cerebrospinal fluid findings and clinical records over a six-month period (March 2009-August 2009). Definite, probable and possible TBM were diagnosed according to published case definitions. Results: TBM was diagnosed in 120/211 patients (57%) with meningitis. In 106 HIV-infected patients with TBM, six-month all-cause mortality was lower in those who received antiretroviral therapy (ART) during TB treatment; hazard ratio = 0.30 (95% CI = 0.08-0.82). Factors associated with inpatient mortality in HIV-infected patients were 1) low CD4<sup>+</sup> count at presentation; adjusted odds ratio (AOR) = 1.4 (95% confidence interval [CI] = 1.03-1.96) per 50 cells/muL drop in CD4<sup>+</sup> count and, 2) higher British Medical Research Council TBM disease grade (2 or 3 versus 1); AOR = 4.8 (95% CI = 1.45-15.87). Interpretation: Starting ART prior to or during TB treatment may be associated with lower mortality in patients with HIV-associated TBM. Advanced HIV and worse stage of TBM disease predict in-hospital mortality in patients presenting with TBM.

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1. **Sample size requirements for separating out the effects of combination treatments: randomised controlled trials of combination therapy vs. standard treatment compared to factorial designs for patients with tuberculous meningitis.**
Wolbers Marcel Trials 2011;12:26-.

BACKGROUNDIn certain diseases clinical experts may judge that the intervention with the best prospects is the addition of two treatments to the standard of care. This can either be tested with a simple randomized trial of combination versus standard treatment or with a 2 x 2 factorial design.METHODSWe compared the two approaches using the design of a new trial in tuberculous meningitis as an example. In that trial the combination of 2 drugs added to standard treatment is assumed to reduce the hazard of death by 30% and the sample size of the combination trial to achieve 80% power is 750 patients. We calculated the power of corresponding factorial designs with one- to sixteen-fold the sample size of the combination trial depending on the contribution of each individual drug to the combination treatment effect and the strength of an interaction between the two.RESULTSIn the absence of an interaction, an eight-fold increase in sample size for the factorial design as compared to the combination trial is required to get 80% power to jointly detect effects of both drugs if the contribution of the less potent treatment to the total effect is at least 35%. An eight-fold sample size increase also provides a power of 76% to detect a qualitative interaction at the one-sided 10% significance level if the individual effects of both drugs are equal. Factorial designs with a lower sample size have a high chance to be underpowered, to show significance of only one drug even if both are equally effective, and to miss important interactions.CONCLUSIONSPragmatic combination trials of multiple interventions versus standard therapy are valuable in diseases with a limited patient pool if all interventions test the same treatment concept, it is considered likely that either both or none of the individual interventions are effective, and only moderate drug interactions are suspected. An adequately powered 2 x 2 factorial design to detect effects of individual drugs would require at least 8-fold the sample size of the combination trial.TRIAL REGISTRATIONCurrent Controlled Trials ISRCTN61649292.

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1. **A case of Pott's disease with epidural abscess and probable cerebral tuberculoma following Bacillus Calmette-Guerin therapy for superficial bladder cancer**
Josephson C.B. Canadian Journal of Infectious Diseases and Medical Microbiology 2010;21(1):-.

Intravesical Bacillus Calmette-Guerin (BCG) immunotherapy is an accepted treatment for transitional cell carcinoma of the bladder. Carcinoma in situ of the bladder progresses to invasive muscular disease in approximately 54% of untreated patients, mandating early initiation of therapy once the diagnosis is confirmed. Should BCG treatment fail, an additional course of BCG combined with interferonalpha, both administered intravesically, is a promising second-line immunotherapy. In greater than 95% of patients, BCG is tolerated without significant morbidity or mortality. However, both early (within three months of the original treatment) and late presentations of systemic infection resulting from intravesical BCG treatment have been described. The present study describes the course of a 75-year-old man with a late presentation of BCG vertebral osteomyelitis, discitis, epidural abscess, bilateral psoas abscesses and probable cerebral tuberculoma, following treatment regimens of intravesical BCG followed by intravesical BCG plus interferon-alpha 2b. &#xa9;2010 Pulsus Group Inc. All rights reserved.

1. **Consensus statement on childhood tuberculosis**
Amdekar Y.K. Indian Pediatrics 2010;47(1):41-55.

Justification: Revised National Tuberculosis Control Program (RNTCP) has focused on adults with smear positivity - a tool not so well used in children with tuberculosis. There is a need to redefine standardization of diagnosis and management protocols for childhood tuberculosis. Process: Indian Academy of Pediatrics constituted a Working Group to develop consensus statement on childhood tuberculosis (TB). Members of the Group were given individual responsibilities to review the existing literature on different aspects of the childhood TB. The group deliberated and developed a consensus which was circulated to all the members for review. Efforts were made to ensure that the recommendations are standardized. Objectives: To produce recommendations and standard protocols for reasonably accurate diagnosis and rational treatment of tuberculosis in children. Recommendations: Fever and / or cough &gt; 2 weeks with loss of weight and recent contact with infectious case should arouse suspicion of TB. Chest X-ray and trial with broad-spectrum antibiotic for 7-10 days is justified. In case of clinical and radiological non-response, Mantoux test and sputum or gastric aspirate for AFB is recommended. If AFB is positive, diagnosis is confirmed. If AFB is negative but chest X-ray is suggestive and Mantoux test is positive, it is a probable case and if these tests are negative, alternate diagnosis must be sought and referral made to an expert. Ideally it is recommended to use 1TU of PPD for Mantoux test but 2 or 5 TU may be acceptable (but less preferred). Cut-off point of 10 mms for natural infection may be used for test done with 1, 2 or 5 TU. There is no linear relation of reaction to tuberculin strength and so no more than 5 TU should be used. BCG test is not recommended. Diagnosis must not be made without an attempt to look for AFB in gastric aspirate or sputum, as it is possible to get AFB even in primary complex. Elisa and PCR tests for TB are not recommended. There is no place for trial of anti-tubercular therapy. Lymphnode enlargement &gt;2 cm with or without typical findings suggestive of TB and failure of antibiotic response demands FNAC for histopathology and bacteriology. Clinical suspicion of tubercular meningitis (TBM) should be confirmed by CSF examination and CT scan though none of these investigations are confirmatory and hence should not be considered in isolation. CSF tests for TB antibody and PCR are not recommended for routine use. Diagnosis of abdominal TB is made on circumstantial evidence and there are no standard guidelines. For treatment, disease is divided into three categories. The Category I and III are recommended for different types of new cases i.e. those who have received treatment for not more than 4 weeks. Category III includes primary pulmonary complex, one site peripheral lympha-denitis and pleural effusion, while all other forms of TB are included in Category I, that corresponds to smear positive TB in adults. This is because AFB is often found in many Category I disease in children. Category II includes defaulters, relapses and failure cases irrespective of the site of disease. Standard protocol is followed for each of these categories. Intermittent thrice weekly therapy with higher dose has been found to be equally effective as daily therapy and so is recommended in DOTS - Direct Observed Therapy Short term. Compliance of treatment must be ensured. Repeat chest X-ray is ideal at the end of therapy. Liver function tests are not routinely recommended. Recommendations are also made for special situations such as MDRTB, TB and HIV and neonate born to mother suffering from TB.

1. **Impact of immigration on pulmonary tuberculosis in Spanish children: a three-decade review.**
del Rosal Teresa The Pediatric infectious disease journal 2010;29(7):648-651.

BACKGROUNDTuberculosis causes significant morbidity and mortality worldwide. In the last years, international travel and immigration have led to important changes in the epidemiology of this disease. Drug resistance has emerged as an important threat to tuberculosis control. Data regarding the impact of immigration and the incidence of drug-resistant strains in children are lacking.METHODSRetrospective review of patients diagnosed with pulmonary tuberculosis at La Paz Children's Hospital in a 30-year period. Data were collected with regard to the clinical, radiologic, microbiologic, and demographic characteristics of patients, and data from the 3 decades of the study were compared using chi test and Fisher exact test.RESULTSA total of 507 cases of tuberculosis were identified, 414 of which had pulmonary involvement. During the study, there was a significant decrease in tuberculous meningitis: 10.4% in 1978-1987, 5.6% in 1988-1997, and 2.9% in 1998-2007 (P < 0.05). The most frequent reason for a consultation was case contact investigation. The adult source case was identified in 64% of patients. We observed an increase in extrafamilial contacts (8% in 1978-1987 and 18% in 1998-2007, P < 0.01), including 4 cases of immigrant caretakers. Tuberculosis in immigrant children has increased with time: 2% in the period 1978-1987, 6% in 1988-1997, and 46% in 1998-2007 (P < 0.001). The primary resistance rate to isoniazid in our population was 6.5%.CONCLUSIONSTuberculosis in our area continues to be a major health problem, especially among foreign-born children. As drug-resistant strains are increasing, initial therapy with 4 drugs is recommended in our population.

1. **Simultaneous scrofuloderma and intracranial tuberculomas: a rare presentation of systemic tuberculosis.**
Wong Kenneth Kien Siang The Australasian journal of dermatology 2010;51(1):39-41.

Tuberculosis can involve multiple organ systems concurrently. We report a case of simultaneous brain tuberculomas and scrofuloderma occurring in the same patient. Skin biopsies confirmed scrofuloderma and the patient was successfully treated for tuberculosis with resolution of the brain masses. This case illustrates the importance of dermatological manifestations of systemic disease as an accessible source for diagnosis and guidance in appropriate therapy.

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1. **The chemotherapy of tuberculous meningitis in children and adults.**
Donald P. R Tuberculosis (Edinburgh, Scotland) 2010;90(6):375-392.

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.

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1. **Therapies for childhood tuberculosis - Current and future approaches**
Pierry C. Paediatric Respiratory Reviews 2010;11:-.

Tuberculosis (TB) in children is an important cause of morbidity and mortality. Multiple therapeutic regimens for different clinical manifestations are in use. The World Health Organization (WHO) has suggested a category-based treatment that has its focus on adult type of TB [1]. DOTS (directly observed therapy, short-course) has become the cornerstone for TB control across the world. There are five key elements for treatment: 1. Government commitment to sustained TB control 2. Case detection by sputum smear microscopy 3. Standardized treatment regimens for all confirmed smearpositive cases 4. Regular uninterrupted supply of essential anti-TB drugs 5. A standardized recording and reporting system DOTS has been adopted by 148 of 210 countries around the world [2]. The main objectives in TB treatment are: 1. To cure the patient of TB (by rapidly eliminating most of the bacilli) 2. To prevent death from active TB or its late effects 3. To prevent relapse of TB (by eliminating the dormant bacilli) 4. To prevent development of drug resistance (by using a combination of drugs) 5. To reduce transmission of TB [1]. Anti-tuberculosis drugs: TB treatment is divided into two phases: \* An intensive initial multidrug phase that aims at killing of the majority of viable bacilli and preventing the emergence of drug resistance. \* A continuation phase: aims at sterilization of TB lesions and prevention of relapse by eradicating the dormant organisms. Fewer drugs are generally used. The action of anti-TB drugs on these different populations may be bactericidal or sterilizing (or both). Bactericidal activity refers to the agent's ability to rapidly kill the actively metabolizing organisms in the sputum of patients with pulmonary TB. Agents can be compared by determining their "Early bactericidal activity" (EBA), defined as the fall in viable colony-forming units (cfu) of Mycobacterium tuberculosis per ml of sputum per day during the first 2 days of treatment [3].There are five "first line" anti-TB agents that have been in use for over 30 years: Isoniazid (INH, H); Rifampicin (RMP, R); Pyrazinamide (Z); Ethambutol (EMB, E) and Streptomycin (S). Regimens: Most children are not smear-positive and do not require four drugs in the initial intensive phase; those who are smearpositive or have a visible cavity on chest radiograph have a high bacillus count and should be treated with four drugs. Also those with severe disease such as extensive lung disease, meningitis or disseminated and Spinal TB with neurological signs, are managed with four drugs in the intensive phase. There is a standard code for TB treatment regimens [4] (Table 1).(Table Presented) Doses: The need for better data on anti-TB drug pharmacokinetics in children is highlighted by the variations in national recommendations for drug doses, particularly those related to INH. Based on several studies it appears that dosage calculations of RPM and EMB are more valid based on body surface area rather than body weight, the latter may be leading to higher doses. Most of the guidelines worldwide recommend the same doses [5] (Table 2). (Table Presented) \* Isoniazid: remains the most important agent, because of its high EBA, outstanding pharmacokinetics and relatively low toxicity. It is rapidly absorbed and has excellent penetration into most body compartments. It is the first agent against which resistance develops. Recent pediatric studies suggest higher doses of INH per kilogram of body weight to achieve similar concentration to those in adults [6]. \* Rifampicin: is a key drug in chemotherapy because it rapidly kills the majority of bacilli in TB lesions and prevents relapse, it has moderate EBA. Absorption is influenced by gastric pH. Pharmacokinetic studies of higher dosages in children are urgently needed [7]. \* Pyrazinamide: has favorable pharmacokinetics and penetrates most tissues, including cerebrospinal fluid; serum levels are related to body weight. Resistance is uncommon but modern studies with molecular methodologies suggest that the prevalence of resistance to PZA may be higher than previously appreciated [3]. \* Ethambutol: Inhibits cell-wall biosynthesis and is effective against actively growing M. tuberculosis. A review of recent publication showed that children have significantly lower peak serum concentrations than adults receiving the same dose; additionally use of higher dose of EMB does not increase ocular toxicity. The recommended dose in children is 20 mg/kg [8-9]. \* Streptomycin: An aminoglycoside, has the highest bactericidal activity in vitro of any anti-TB agent, though it has low EBA. Its aim is to prevent resistance to companion drugs. It can cause otovestibular damage and nephrotoxicity. \* Corticosteroids: While not an anti-TB agent per se, is used in meningitis, endobronchial TB, enlarged lymph nodes that compress the tracheobronchial tree, localized emphysema, or severe pulmonary disease. It can also be used in tamponade with TB-related pericardial effusion. The most frequently used drug is prednisone, at a dose of 1 to 2 mg/kg/day for 4 to 6 weeks with gradual tapering (dose should be reduced over 1-2 weeks before stopping) [1]. Adverse effects: Are less common than in adults. The most frequent is hepatotoxicity, which can be caused by INH, RMP or Z. An asymptomatic mild elevation of serum liver enzymes is not an indication for cessation of treatment, but hepatomegaly and jaundice should lead to discontinuation of the potentially hepatotoxic drugs. If treatment needs to be completed, non-hepatotoxic drugs should be utilized, such as: ethambutol, an aminoglycoside and a fluoroquinolone.

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1. **[Onset of neurological symptoms during tuberculosis treatment: description of two cases].**
Arquinio Luis Enfermedades infecciosas y microbiologia clinica 2010;28(10):753-755.

1. **Neurologic manifestations of paradoxical tuberculosis-associated immune reconstitution inflammatory syndrome: A case series**
Pepper D.J. Clinical Infectious Diseases 2009;48(11):-.

Background. Paradoxical neurologic tuberculosis-associated immune reconstitution inflammatory syndrome (TB-IRIS) is a potentially life-threatening condition that occurs within 3 months after starting combination antiretroviral therapy (ART). The reports in the published literature are anecdotal, and the prevalence and outcomes of neurologic TB-IRIS are unknown. Methods. We prospectively assessed patients with suspected TB-IRIS from June 2005 through October 2007 at our hospital in Cape Town, South Africa. We defined paradoxical TB-IRIS and paradoxical neurologic TB-IRIS with use of consensus clinical case definitions. We collected data on tuberculosis diagnosis, ART, details of TB-IRIS diagnosis, other opportunistic infections, corticosteroid use, and outcome. Results. We reviewed 279 patients with suspected TB-IRIS, 54 (19%) of whom had suspected neurologic TB-IRIS, and 225 (81%) of whom had suspected non-neurologic TB-IRIS. Paradoxical TB-IRIS was diagnosed in 190 patients; 23 (12%) of these 190 patients had neurologic TB-IRIS (95% confidence interval, 7%-17%). Eight had meningitis, 7 had tuberculoma, 5 had both tuberculoma and meningitis, and 3 had radiculomyelopathy. Twenty (87%) of the 23 patients with neurologic TB-IRIS required hospital admission (median duration, 12 days; interquartile range, 6-24 days), and 21 (91%) received corticosteroids (median duration, 58 days; interquartile range, 29-86 days). Outcomes 6 months after the initial assessment for neurologic deterioration were as follows: 16 (70%) of the patients were alive (10 of these patients had documented full physical and mental recovery), 3 (13%) were dead, and 4 (17%) were lost to follow-up. Conclusions. Paradoxical neurologic TB-IRIS accounts for 12% of paradoxical TB-IRIS cases. Neurologic TB-IRIS causes considerable short-term morbidity but has reasonable long-term outcomes. Further research is needed to devise optimal diagnostic and management strategies for patients with tuberculosis who experience neurologic deterioration after starting ART. &#xa9; 2009 by the Infectious Diseases Society of America. All rights reserved.

1. **Paradoxical reaction in tubercular meningitis resulting in involvement of optic radiation.**
Monga Parveen K. Indian journal of ophthalmology 2009;57(2):139-141.

A 25-year-old woman was diagnosed to have tubercular meningitis (TBM) with a right parietal infarct. She responded well to four-drug anti-tubercular treatment (ATT), systemic steroids and pyridoxine. Steroids were tapered off in one and a half months; she was put on two-drug ATT after two months. Six months after initial diagnosis she presented with sudden, bilateral visual loss. Vision was 3/200 with afferent pupillary defect and un-recordable field in the right eye; vision was 20/60 in the left eye, pupillary reaction was sluggish and the field showed a temporal hemianopia. On reintroduction of systemic corticosteroids vision improved (20/120 in right eye and 20/30 in left eye) within three days; the field defects improved sequentially to a left homonymous hemianopia, then a left homonymous inferior quadrantonopia. A diagnosis of TBM, on treatment, with bilateral optic neuritis, and right optic radiation involvement was made. Since the patient had been off ethambutol for four months, the optic neuritis and optic radiation lesion were attributed to a paradoxical reaction to tubercular allergen, corroborated by prompt recovery in response to corticosteroids. This is the first report of optic radiation involvement in a paradoxical reaction in neuro-tuberculosis in a young adult.

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1. **Tuberculous meningitis in HIV-infected and non-infected patients: comparison of cerebrospinal fluid findings.**
Cecchini D. The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease 2009;13(2):269-271.

We performed a retrospective comparison of cerebrospinal fluid (CSF) characteristics and drug susceptibility profile in human immunodeficiency virus (HIV) infected and non-infected patients with a diagnosis of tuberculous meningitis. HIV-infected patients had a higher frequency of non-inflammatory CSF (absence of pleocytosis) and of infection by multidrug-resistant strains of Mycobacterium tuberculosis. Protein CSF levels were lower in HIV-infected patients, while and glucose concentration was similar in both groups. Hospital mortality was significantly higher in HIV-infected patients (63.3% [64/101] vs. 17.5% [7/40]).

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1. **[Macular tuberculoma and optic neuritis: rare association with tuberculosis meningoencephalitis].**
Laktaoui A. Journal francais d'ophtalmologie 2009;32(9):673-678.

INTRODUCTIONTuberculosis is an endemic disease responsible for death and morbidity in developing countries.OBSERVATIONA 50-year-old man with no medical history was admitted to the emergency department for meningism associated with fever and confusion. The ophthalmic exam showed a decline in left visual acuity, reduced to light perception, VIth nerve left oculomotor paralysis, ocular fundus demonstrating a yellow tumor located on the posterior segment, measuring 1.5-2mm, papillomatous and prominent in the vitreous cavity. Fluorescein angiography showed a peritumoral choroiditis area, miliary tubercles of the choroid, and sectorial papillomatous edema. Color retinography unmasked inflamed posterior vitreous areas. Echography demonstrated a 4- to 5-mm oval hyperechogeneous and calcified tumor along with hyperechogeneous vitreous areas. Lumbar puncture showed lymphocytic meningitis associated with hyponatremia. The CT scan and MRI demonstrated optic neuritis. The antibiotic therapy was initiated and the outcome was favorable.CONCLUSIONThis case report shows the importance of systematic ocular fundus in the presence of systemic tuberculosis and outlines the assessment of color retinography to unmask vitreous lesions. It shows the importance of radiological imaging in the semiological study of orbital and cerebral lesions.

1. **A case of oculomotor nerve palsy and choroidal tuberculous granuloma associated with tuberculous meningoencephalitis.**
Moon Sunghyuk Korean journal of ophthalmology : KJO 2008;22(3):201-204.

We report a rare case of oculomotor nerve palsy and choroidal tuberculous granuloma associated with tuberculous meningoencephalitis. A 15-year-old male visited our hospital for an acute drop of the left eyelid and diplopia. He has been on anti-tuberculous drugs (isoniazid, rifampin) for 1 year for his tuberculous encephalitis. A neurological examination revealed a conscious clear patient with isolated left oculomotor nerve palsy, which manifested as ptosis, and a fundus examination revealed choroidal tuberculoma. Other anti-tuberculous drugs (pyrazinamide, ethambutol) and a steroid (dexamethasone) were added. After 3 months on this medication, ptosis of the left upper eyelid improved and the choroidal tuberculoma decreasedin size, but a right homonymous visual field defect remained. When a patient with tuberculous meningitis presents with abrupt onset oculomotor nerve palsy, rapid re-diagnosis should be undertaken and proper treatment initiated, because the prognosis is critically dependent on the timing of adequate treatment.

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1. **Tuberculous meningoencephalitis in a pregnant woman presenting 7 years after removal of a cerebral granuloma**
Liu C. European Journal of Clinical Microbiology and Infectious Diseases 2008;27(3):233-236.

We describe the unusual case of a young woman with a history of seizures and a granulomatous, likely tuberculous brain lesion that was surgically removed. She had an uneventful recovery without any additional therapy other than anti-epileptics. Seven years later, she presented during pregnancy with culture-confirmed tuberculous meningoencephalitis. This case highlights the spectrum of tuberculous central nervous system disease and the challenges in diagnosis. &#xa9; 2007 Springer-Verlag.

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1. **[A meningitis case of Brucella and tuberculosis co-infection].**
Karsen Hasan Mikrobiyoloji bulteni 2008;42(4):689-694.

Turkey is located at an endemic area for brusellosis and tuberculosis which are both important public health problems. Meningitis caused by Brucella and Mycobacterium spp. may be confused since the clinical and laboratory findings are similar. In this report, a meningitis case with Brucella and tuberculosis co-infection has been presented. A 19-years-old woman was admitted to our clinic with severe headache, fever, vomiting, meningeal irritation symptoms, confusion and diplopia. The patient was initially diagnosed as Brucella meningitis based on her history (stockbreeding, consuming raw milk products, clinical symptoms concordant to brucellosis lasting for 4-5 months), physical examination and laboratory findings of cerebrospinal fluid (CSF). Standard tube agglutination test for brucellosis was positive at 1/80 titer in CSF and at 1/640 titer in serum, whereas no growth of Brucella spp. was detected in CSF and blood cultures. Antibiotic therapy with ceftriaxone, rifampicin and doxycyclin was started, however, there was no clinical improvement and agitation and confusion of the patient continued by the end of second day of treatment. Repeated CSF examination yielded acid-fast bacteria. The patient was then diagnosed as meningitis with double etiology and the therapy was changed to ceftriaxone, streptomycin, morphozinamide, rifampicin and isoniazid for thirty days. Tuberculosis meningitis was confirmed with the growth of Mycobacterium tuberculosis on the 14th day of cultivation (BACTEC, Becton Dickinson, USA) of the CSF sample. On the 30th day of treatment she was discharged on anti-tuberculous treatment with isoniazid and rifampicin for 12 months. The follow-up of the patient on the first and third months of treatment revealed clinical and laboratory improvement. Since this was a rare case of Brucella and tuberculosis co-infection, this report emphasizes that such co-infections should be kept in mind especially in the endemic areas for tuberculosis and brucellosis.

1. **[Neurotuberculosis: a continuing clinical challenge].**
Mackert B.-M Der Nervenarzt 2008;79(2):153-166.

In Germany neurotuberculosis is quite rare. Familiarity with the disease is nonetheless important because of many differential diagnoses and therapeutic implications. The diagnosis of neurotuberculosis is made by considering of clinical presentation, CSF, and cerebral imaging. Early diagnosis, prompt initiation of effective antitubercular therapy, and clinical staging are necessary for establishing a long-term treatment prognosis. The results of neurotuberculosis therapy are often unsatisfactory despite the availability of effective drugs. Lasting damage or death can be averted in fewer than half of the patients. Studies now confirm that early adjuvant corticoid therapy reduces lethality and morbidity. Resistant new strains of the pathogen, Mycobacterium tuberculosis, complicate therapy. Recent discoveries especially in diagnosis and therapy are explained using case evidence.

1. **Simultaneous tuberculous meningoencephalitis in two siblings.**
Meyer Sascha Wiener medizinische Wochenschrift (1946) 2007;157(1-2):37-42.

UNLABELLEDThe high morbidity and mortality of tuberculous meningoencephalitis (TBM) warrants an early diagnosis and treatment. BCG vaccine has been proven to reduce the incidence of disseminated disease in children. We report on two siblings (2-year-old boy and 4-year-old girl) with simultaneous TBM, whose parents originated from Kosovo, Albania, but presently reside in Germany. Early diagnosis of TBM was delayed, and at first the misdiagnosis of viral meningoencephalitis was made. Antituberculosis treatment was not initiated despite profound hyponatremia, hydrocephalus, and signs of inflammatory cerebral disease. After establishing the diagnosis of TBM, the boy died from antituberculosis, drug-induced hepatic failure; the sister survived with severe neurological deficits. Contact tracing revealed that TB had been transmitted by a household contact person with proven pulmonary TB who had refused antituberculosis treatment. A thorough contact investigation including tuberculin skin testing to identify children at risk for TB in the vicinity of this patient was not carried out. These case reports demonstrate an unusual simultaneous occurrence of TBM in a brother and sister. It draws attention to the importance of TBM as a differential diagnosis in children with suspected viral meningoencephalitis.CONCLUSIONSTo prevent severe neurological sequelae, early antituberculosis therapy should be considered in infants and children with a clinical impression of meningitis in the context of cerebrospinal fluid white blood cell count of less than 500 cells/microl and lymphocytic predominance, hyponatremia, and possible hydrocephalus. This notion is especially true for children originating from high-endemicity countries for TB. A rigid implementation of antituberculosis treatment of infected individuals and contact tracing is mandatory in order to prevent dissemination of TB in the community. The use of BCG vaccine should be considered in children at high risk for TB infection because of its potential to reduce disseminated TB.

1. **[Aseptic cerebral venous thrombosis and multiple cerebral tuberculomas associated with pulmonary miliary tuberculosis].**
Messouak O. Revue neurologique 2007;163(2):238-240.

INTRODUCTIONSevere pulmonary tuberculosis may be complicated by deep vein thrombosis due to a state of hypercoagulability.OBSERVATIONWe report a case of pulmonary miliary tuberculosis associated with cerebral venous thrombosis and multiple intracranial tuberculomas. A 65-year-old woman developed a confusional syndrome one week after starting treatment for pulmonary military tuberculosis. Neuroimaging reveals a thrombus in the right lateral sinus and multiple silent intracranial tuberculoma.CONCLUSIONThe patient was given anticoagulants and fully recovered.

1. **[Clinical practice guidelines from the Andalusian Society of Infectious Diseases (SAEI) for the treatment of tuberculosis].**
Domínguez-Castellano Angel Enfermedades infecciosas y microbiologia clinica 2007;25(8):519-534.

The therapeutic scheme for initial pulmonary tuberculosis recommended by the SAEI is as follows: Initial phase, isoniazid, rifampin and pyrazinamide given daily for 2 months. In HIV(+) patients and immigrants from areas with a rate of primary resistance to isoniazid > 4%, ethambutol should be added until susceptibility studies are available. Second phase (continuation phase): rifampin and isoniazid, given daily or intermittently for 4 months in the general population. HIV(+) patients (< or = 200 CD4) and culture-positive patients after 2 months of treatment should receive a 7-month continuation phase. A 6-month regimen is recommended for extrapulmonary tuberculosis, with the exception of tuberculous meningitis, which should be treated for a minimum of 12 months and bone/joint tuberculosis, treated for a minimum of 9 months. Treatment regimens for multidrug resistant tuberculosis are based on expert opinion. These would include a combination of still-useful first-line drugs, injectable agents, and alternative agents, such as quinolones. Patients who present a special risk of transmitting the disease or of non-adherence should be treated with directly observed therapy.

1. **Challenges in diagnosis, treatment and follow-up of patients presenting with central nervous system infections in a resource-limited setting**
Leligdowicz A. McGill Journal of Medicine 2006;9(1):39-48.

Central Nervous System (CNS) infections are associated with significant mortality and morbidity. Accurate diagnosis is necessary for prompt treatment and increased chances of survival. However, there are many challenges to correct diagnoses in resource-limited settings, including the HIV epidemic, late presentation of symptomatic individuals, limited availability of laboratory diagnostic tests as well as treatment, and inadequate access to funds accompanied by lack of financial support from developed countries. This article presents case reports of patients admitted to the Mulago Hospital in Kampala, Uganda that exemplify challenging diagnoses of tuberculous meningitis (TBM), cryptococcal meningitis (CM), toxoplasmosis, and primary CNS lymphoma (PCNSL). Also included is a literature review of the pathology, diagnosis, and treatment of TBM, CM, toxoplasmosis, and PCNSL in immunocompromised patients. Copyright &#xa9; 2006 by MJM.

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1. **[Treatment of tuberculous meningitis].**
Steichen O. Revue neurologique 2006;162(5):581-593.

INTRODUCTIONTuberculous meningitis and brain tuberculomas are currently rare in the western world but remain serious. Improved outcome requires early recognition and treatment of these conditions.STATE OF ARTTreatment is usually begun before diagnostic confirmation. Therapeutic principles are now better defined thanks to recent recommendations and studies. Antituberculous therapy begins with two months of a combination of four drugs: isoniazid, rifampicin, ethambutol and pyrazinamid. Then follows a longer phase of bitherapy with isoniazid and rifampicin, lasting at least four months but usually extended to seven or ten months as a precaution. Patients at risk of toxic neuropathy should receive pyridoxine supplementation. Corticosteroids must be systematically added during the first eight weeks of treatment, beginning with high dose before progressive tapering. Hyponatremia is common, often induced by emesis and cerebral salt wasting syndrome. Therefore saline supply rather than water restriction is required. Non-obstructive hydrocephaly can usually be managed with diuretic therapy including acetazolamid, sometimes complemented by serial lumbar punctures. Neurosurgical interventions are rarely needed. Monitoring of treatment tolerance and efficacy is mainly clinical. Central nervous system imaging and cerebro-spinal fluid analysis are only required to explain clinical deterioration.CONCLUSIONWith adequate and prompt anti-tuberculous, anti-inflammatory and supportive treatment, the prognosis of central nervous system tuberculosis can be greatly improved.

1. **A registry of tuberculous meningitis in Hong Kong.**
Lau K. K The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease 2005;9(12):1391-1397.

BACKGROUNDA prospective observational study of the presentation, diagnosis, treatment and outcome of tuberculous meningitis (TBM).METHODSDemographic characteristics, clinical information, treatment and progress of TBM patients were followed. Their outcomes were ascertained every 6 months for 3 years after diagnosis. Prognostic factors associated with death or full recovery were examined using multivariate Cox's and logistic regression models, respectively.RESULTSBetween 1993 and 2000, 166 TBM patients were recruited. Their mean age was 42.9, 153 were Chinese and 81 were males; 92% received HRZS (H = isoniazid; R = rifampicin; Z = pyrazinamide; S = streptomycin), HRZE (E = ethambutol) or HRZES. Steroids were given to 105 patients, with no significant effect on outcome. After 3 years of follow-up, 110 patients had completely recovered, 20 survived with disability and 26 died. Death was significantly associated with older age, lower cerebrospinal fluid (CSF) lymphocyte and poorer consciousness levels at the time of presentation, while full recovery was associated with younger age, being female and absence of complications.CONCLUSIONSRelatively good outcomes of TBM cases were documented in this Hong Kong study with a case-fatality ratio of 15.7% (26/166) up to 3 years. Early recognition, diagnosis and administration of effective treatment regimens were probably the most important factors in reducing mortality and morbidity.

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1. **Effect of antituberculosis drug resistance on response to treatment and outcome in adults with tuberculous meningitis.**
Thwaites Guy E. The Journal of infectious diseases 2005;192(1):79-88.

BACKGROUNDTuberculous meningitis (TBM) caused by Mycobacterium tuberculosis resistant to 1 or more antituberculosis drugs is an increasingly common clinical problem, although the impact on outcome is uncertain.METHODSWe performed a prospective study of 180 Vietnamese adults admitted consecutively for TBM. M. tuberculosis was cultured from the cerebrospinal fluid (CSF) of all patients and was tested for susceptibility to first-line antituberculosis drugs. Presenting clinical features, time to CSF bacterial clearance, clinical response to treatment, and 9-month morbidity and mortality were compared between adults infected with susceptible and those infected with drug-resistant organisms.RESULTSOf 180 isolates, 72 (40.0%) were resistant to at least 1 antituberculosis drug, and 10 (5.6%) were resistant to at least isoniazid and rifampicin. Isoniazid and/or streptomycin resistance was associated with slower CSF bacterial clearance but not with any differences in clinical response or outcome. Combined isoniazid and rifampicin resistance was strongly predictive of death (relative risk of death, 11.63 [95% confidence interval, 5.21-26.32]) and was independently associated with human immunodeficiency virus infection.CONCLUSIONSIsoniazid and/or streptomycin resistance probably has no detrimental effect on the outcome of TBM when patients are treated with first-line antituberculosis drugs, but combined isoniazid and rifampicin resistance is strongly predictive of death.

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1. **It is too early to discount the contribution of isoniazid to the treatment of tuberculous meningitis.**
Seaworth Barbara J. The Journal of infectious diseases 2005;192(1):10-12.

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1. **[Tuberculoma and tuberculous meningeal-radiculitis with paradoxical progression during treatment].**
Rabar D. Presse medicale (Paris, France : 1983) 2005;34(1):32-34.

INTRODUCTIONNeuromeningeal tuberculosis of deleterious, paradoxical, progression despite appropriate antibiotic therapy is rare.OBSERVATIONAn immunocompetent woman exhibited an immediately disseminated form of tuberculosis with progressive neurological involvement associating expanding intracranial tuberculomas and meningeal-radiculitis despite adapted anti-tuberculosis quadritherapy.DISCUSSIONDuring anti-tuberculosis therapy clinical worsening is rare, particularly when 2 different manifestations are associated and the worsening occurs in an immunocompetent patient. This possibility should be systematically evoked in such cases. The explanation of this phenomenon is still unclear.

1. **[Tuberculoma complicating tuberculous meningitis: description of one paediatric case].**
Ruggeri C. Minerva pediatrica 2005;57(5):329-332.

Intracranial tuberculoma is a possible complication of meningeal, miliary or pulmonary tuberculosis. In developing countries it represents 30% of space-occupying intracranial lesions, in industrialised countries only 0.1-0.2%. One recently recognised phenomenon is the development ex novo or the enlargement of the tuberculoma during antitubercular chemo-antibiotic therapy. Here we report the clinical case of an immunocompetent Italian baby girl who presented an intracranial tuberculoma during tuberculous meningitis. We underline how such an event is possible, the need for early neuroradiological evaluation and its favourable course, maintaining adequate antitubercular therapy associated with steroid therapy.

1. **Cranial-epidural tuberculosis presenting as a scalp swelling.**
Shahat Abdul Hameed Surgical neurology 2004;61(5):464-.

BACKGROUNDUnlike the brain tuberculoma, tubercular osteomyelitis of the skull is very rare and not sufficiently described in the literature. Awareness of this entity makes diagnosis possible.CASE DESCRIPTIONSTwo unique cases of cranial and epidural tuberculosis (TB) with absence of intradural and brain involvement are presented. Both patients presented with scalp swellings but extending through the calvarium into the epidural space. Histologic/bacteriologic confirmation of tuberculosis was obtained from biopsy specimens. Magnetic resonance imaging (MRI) findings of this rare lesion are described for the first time.CONCLUSIONSInflammatory scalp lesions with skull involvement and epidural extension should be investigated for tuberculous etiology. With early diagnosis and a combination of surgical and medical management, all cases of skull tuberculosis are potentially curable.

1. **Prognostic indicators in patients with intracranial tuberculoma: a review of 102 cases.**
Wasay M. JPMA. The Journal of the Pakistan Medical Association 2004;54(2):83-87.

OBJECTIVETo see the characteristics, course and outcome of patients suffering from intracranial tuberculoma.METHODSRetrospective review of 102 patients diagnosed as intracranial tuberculoma at a tertiary care center over 10 years.RESULTSA total of 102 cases were seen with an age range of 1 to 75 years (mean, 30 years). Predisposing factors included Diabetes mellitus (8 patients) and pregnancy or puerperium (7 patients). Five pediatric patients had tuberculoma despite documented BCG vaccination. Fever (59%), headache (57%), meningeal irritation (36%) were the commonest presenting features; one-third of patients were drowsy or comatosed at presentation. Cerebrospinal fluid analysis was performed in 63 patients, of whom 88% had elevated protein, 83% had low glucose, and 84% had pleocytosis (one-third with neutrophilia). Forty-nine (50%) patients had clinical or laboratory evidence of concomitant tuberculous meningitis. Chest radiographs showed active or old tuberculous infection (25%), with a miliary pattern in 20%. Two-thirds of subjects had multiple tuberculomas (mean, 4.5 lesions per patient) on contrast CT or MRI scan. Hydrocephalus was present in 37 (37%) patients of which 21 required shunt surgery. Thirty-nine patients had > 9 months of follow up; 17 patients showed complete recovery, 20 patients had partial recovery, and 2 patients had no response. Coma at presentation and miliary pattern on chest X-ray were predictors of poor prognosis.CONCLUSIONThe study demonstrate that fever, headache, signs of meningeal irritation and cranial nerve palsies are common presenting features. Complete recovery was seen in 40% patients. Coma and military TB are predictors of poor prognosis.

1. **Breakthrough neurological manifestation during appropriate antituberculous therapy of miliary tuberculosis.**
Lolekha Rangsima The Southeast Asian journal of tropical medicine and public health 2003;34(3):634-635.

We report a 20-month-old girl with miliary pulmonary tuberculosis and normal neurological findings. While on treatment with isoniazid, rifampicin, pyrazinamide, and ethambutol for 1 month, she developed weakness of the lower extremities without meningism or altered consciousness. A computerized tomogram revealed tuberculomas and basal arachnoiditis. The cerebrospinal fluid findings were compatible with tuberculous meningitis. She responded well to systemic corticosteroids.

1. **[An adult case of tuberculous meningitis].**
Nakao Shoko Nihon Kokyuki Gakkai zasshi = the journal of the Japanese Respiratory Society 2003;41(4):294-299.

A 36-year-old man was referred to our hospital with complaints of high fever and headache. A diagnosis of miliary tuberculosis with tuberculous meningitis was made. He was treated with isoniazid (400 mg/day), rifampicin (300 mg/day), ethambutol (750 mg/day), pyrazinamide (1.0 g/day) and prednisolone (60 mg/day). However, he lost consciousness because of hydrocephalus on the second day of hospitalization. Emergency cerebrospinal fluid drainage improved his neurological symptoms. After two months, he again complained of headache with nausea and double vision. Numerous tuberculomas were found not only in the cerebrum but also in the liver, the spleen and the retina. Recurrent hydrocephalus was treated with a V-P shunt, and combination therapy with four antituberculous agents was maintained for 18 months. He was discharged in a healthy condition, although a mild left facial palsy remained. In addition, we examined the inflammatory cytokine levels in both the CSF and the serum over the period of the patient's hospitalization. We concluded that the cytokine levels in the CSF may be associated with the progress and the prognosis of tuberculous meningitis.

1. **Long-term follow up of childhood tuberculous meningitis.**
Schoeman J. Developmental medicine and child neurology 2002;44(8):522-526.

The purpose of the present study was to determine the long-term outcome of 76 children (40 females and 36 males) diagnosed and treated with modern antituberculosis drugs. The median age of the children on admission was 29.5 months and on follow-up 9 years. Antituberculosis therapy consisted of daily isoniazid (20 mg/kg), rifampicin (20 mg/kg), ethionamide (20 mg/kg), and pyrazinamide (40 mg/kg) for 6 months. Twenty-three children received daily prednisone (2-4 mg/kg) for the first month of treatment. Raised intracranial pressure was actively monitored and treated. Patients with non-communicating hydrocephalus received ventriculo-peritoneal shunts shortly after admission while communicating hydrocephalus was treated with oral acetazolamide (100 mg/kg/day) and furosemide (1 mg/kg/day) in 3-4 divided doses. Communicating hydrocephalus that did not respond to this regimen within the first month of treatment also underwent ventriculo-peritoneal shunting. Only 20% of children were functionally completely normal at follow-up. Main areas of functional deficit were cognitive impairment (80%), poor scholastic progress (43%), and emotional disturbance (40%). Twenty-five per cent of children had evidence of motor impairment, but all could walk and only 5 of 76 children (6% of total) were unable to run. One child was blind but no child had sensori-neural deafness. It was concluded that these disabilities in children from mainly deprived socioeconomic backgrounds have serious implications for their future social, academic, and career prospects. A high index of suspicion of TBM in high tuberculosis incidence communities will help prevent the morbidity documented in this study.

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1. **Prognosis of tuberculous meningitis in adults in the era of modern antituberculous chemotherapy.**
Wang Jann-Tay Journal of microbiology, immunology, and infection = Wei mian yu gan ran za zhi 2002;35(4):215-222.

This study reviewed the clinical manifestations and outcome of tuberculous meningitis in the era of modern antituberculous chemotherapy and applied these data in assessing the role of clinical staging evaluated 30 days after treatment in predicting long-term outcome. A total of 41 adult patients with tuberculous meningitis hospitalized at a university hospital in Taiwan from June 1994 through August 1999 were included in this retrospective study. Their age ranged from 16 to 80 years (median, 41 years), and 17 (41.5%) patients had had a variety of underlying immunocompromising diseases. Fever (90%), headache (75.6%), neck stiffness (68.3%), altered consciousness (26.8%), and nausea and/or vomiting (26.8%) were the leading initial presentations. During the treatment course, 19 patients experienced new neurologic complications. The overall case fatality rate was 9.8% and morbidity rate 56.1%. More advanced clinical stage evaluated at 30 days after initiation of antituberculous chemotherapy and positive cerebrospinal fluid culture for Mycobacterium tuberculosis were the only 2 factors significantly associated with a worse long-term prognosis. Results indicate that tuberculous meningitis is associated with a high morbidity, consisting of minor and major neurologic sequelae, despite modern antituberculous chemotherapy. In addition, more advanced clinical staging evaluated at 30 days after the start of antituberculous chemotherapy and a positive cerebrospinal fluid culture for M. tuberculosis were associated with a poor prognosis.

1. **Novel treatment of meningitis caused by multidrug-resistant Mycobacterium tuberculosis with intrathecal levofloxacin and amikacin: case report.**
Berning S. E Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 2001;32(4):643-646.

We report the case of a 25-year-old HIV-negative man with disseminated multidrug-resistant tuberculosis (MDRTB), who-on a retreatment regimen-experienced total resolution of TB miliary disease, but progressive TB meningitis. Therefore, intrathecal treatment with amikacin and levofloxacin was instituted, with successful clinical and microbiological results.

1. **Spinal tuberculosis: Early surgical treatment combined with medical treatment**
Fuster S. Medicina Clinica 2001;117(12):457-459.

Background: Spinal tuberculosis can produce kyphosis with neurological deficit, despite antibiotic treatment. When there is no response to medical treatment, the recommended procedure is debridement and interbody fusion with bone autograft. The biological characteristics of Mycobacterium tuberculosis do not prevent osteosynthesis of the infected bone from being performed. Patients and Method: Five patients with spinal tuberculosis and neurological deficit underwent debridement, interbody fusion and anterior osteosynthesis in addition to medical treatment. In order to ensure stability, posterior fusion was also performed in three patients. All 5 patients displayed weakness and paralysis of their lower extremities, two patients suffered an L4 radiculopathy, one developed paraparesia and one was excluded due to a short follow-up. Mean value of vertebral kyphosis was 22,8degree and mean follow-up was 3,1 years. Results: No patient had septic loosening or progression of the disease. Correction of kyphosis was 104,5% postoperatively and 80,5% at the end of follow-up. All patients, apart from one with an L4 radiculopathy, exhibited neurological recovery. Conclusions: Anterior instrumentation allows spinal decompression, septic focus debridement, deformity correction and autologous bone grafting. In severe kyphotic flattening, it is advisable to associate a limited posterior arthrodesis. When pathological fractures appear or there is no response to antibiotic treatment, the combination of medical and surgical treatment improves patients' outcome.

1. **The effect of adjuvant steroid treatment on serial cerebrospinal fluid changes in tuberculous meningitis.**
Schoeman J. F Annals of tropical paediatrics 2001;21(4):299-305.

Three recent studies found that corticosteroids improve clinical outcome and mortality in tuberculous meningitis (TBM), although the exact mechanism of action of the drug remains speculative. A number of reports on the effect of corticosteroids on cerebrospinal fluid (CSF) findings in TBM have been published, often with conflicting results regarding serial cell counts and protein levels. As part of a controlled, randomized trial on the effect of oral prednisone on outcome in childhood TBM at our institution, CSF was collected and analysed weekly during the 1st month of treatment. We found no significant difference in serial CSF cell counts between the steroid and non-steroid groups in the study. However, the steroid group had significantly lower CSF protein and globulin levels after the 1st month of treatment, and a more steady rise in CSF glucose levels than the non-steroid group. Knowledge of the different CSF responses during the course of anti-tuberculosis therapy is important in clinical decision-making.

1. **Tuberculous meningitis: is a 6-month treatment regimen sufficient?**
van Loenhout-Rooyackers J. H The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease 2001;5(11):1028-1035.

SETTINGThe British Thoracic Society and the American Thoracic Society advise 12 months treatment for tuberculous meningitis, with at least isoniazid (H), rifampicin (R) and pyrazinamide (Z).OBJECTIVETo establish whether a 6-month treatment regimen for tuberculous meningitis is equally as effective as longer treatment.METHODMedline search for papers published between 1978 and 1999.INCLUSION CRITERIAstudy populations of patients with tuberculous meningitis in whom the diagnosis was confirmed with clinical, cerebrospinal fluid and epidemiological findings; a treatment regimen with at least HRZ and at least 12 months of follow-up after the completion of treatment.OUTCOME MEASUREthe number of relapses.RESULTSThere were four 6-month treatment regimens (G6) and seven longer treatment regimens (G>6); 160/197 (81%) patients completed the 6-month treatment regimens, while 577/675 (85%) completed the longer-term regimens. The clinical stage of patients in the G6 group was poorer than in the G>6 group. Relapse occurred in two out of 131 (1.5%) G6 and in 0 out of 591 G>6 patients.CONCLUSIONAlthough no studies have compared 6-month treatment regimens with longer treatment, it can be concluded on the basis of this literature review that 6-month treatment is sufficient for tuberculous meningitis with fully susceptible mycobacteria.

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1. **Tuberculous meningoencephalitis in HIV-seronegative patients: variety of clinical presentation and impact on diagnostics and treatment.**
Kassubek J. Acta neurologica Scandinavica 2001;104(6):389-396.

UNLABELLEDTuberculous meningoencephalitis (TBM), an infrequent disease in Western European countries, shows a wide heterogeneity of clinical symptoms.MATERIAL AND METHODSWe present 4 patients (age range 42-72 years) with the definite diagnosis of isolated TBM. All patients were HIV-seronegative, only 1 patient was known to be immunoincompetent on admission due to acute myelocytic leukemia; other reasons for immune suppression were detected in 2 other patients (leukemia and idiopathic CD4+ T-lymphocytopenia, respectively).RESULTSThe diagnosis of TBM was confirmed in 3 cases by culture from CSF, in 1 case Mycobacterium tuberculosis was proven only in tracheal aspirate. In 1 patient M. bovis was found, which is an extremely rare cause of TBM in Germany. We report the contributions of different diagnostic tools (CSF analysis, neuroimaging) in reaching the presumptive diagnosis and in monitoring the further course. All patients developed neurological complications despite prompt tuberculostatic treatment. Three of the patients presented a chronic severe loss of consciousness of unclear origin.CONCLUSIONThe possible causative relationships of these complications and their impact on the prognosis are discussed.

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1. **Tuberculous peritonitis--reports of 26 cases, detailing diagnostic and therapeutic problems.**
Demir K. European journal of gastroenterology & hepatology 2001;13(5):581-585.

OBJECTIVETo evaluate the clinical presentation, biochemical (ascites and serum) and laparoscopic findings, and to assess the efficacy of triple antituberculous therapy without rifampicin for 6 months in patients with tuberculous peritonitis.METHODSTwenty-six tuberculous peritonitis patients (11 male, 15 female) with a mean age of 34.8 +/- 3.4 years (range 14-77) were assessed with regard to diagnostic and therapeutic features.RESULTSThe most common symptoms and signs were abdominal pain (92.3%) and ascites (96.2%), respectively. Tuberculin skin test (TST) was positive in all patients. An abnormal chest radiography suggestive of previous tuberculosis was present in five patients (19.2%), and two patients (7.7%) had extra-peritoneal (cerebral, pericardial) active tuberculous involvement. In 24 of the 25 patients who underwent laparoscopy with directed biopsy, whitish nodules suggested tuberculous peritonitis; 76% of the biopsy specimens revealed caseating, 20% non-caseating granulomatous inflammation, and 4% non-specific findings. The ascitic fluid of one patient (3.8%) was positive for acid-resistant bacilli, and culture was positive in two patients (7.7%). Twenty-four of the patients were treated for 6 months with isoniazid, streptomycin (total dose 40 g) and pyrazinamide (for the first 2 months and then substituted with ethambutol). Eighteen patients also received methyl prednisolone, initially 20 mg/day, for 1 month. The follow-up period was 19 +/- 1.7 months after the end of therapy (range 6-36). Ascites and abdominal pain abated earlier in patients on steroid therapy. All but two of the 24 patients responded to treatment.CONCLUSIONNon-invasive tests such as acid-fast stain and culture of the ascitic fluid are usually insufficient, hence invasive laparoscopy and peritoneal biopsy are necessary for the diagnosis of tuberculous peritonitis if non-invasive tests such as ascites adenosine deaminase activity measurement are not easily available. Triple therapy without rifampicin for 6 months is sufficient to treat tuberculous peritonitis.

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1. **Clinical profile of neurobrucellosis--a report on 12 cases from Bikaner (north-west India).**
Kochar D. K The Journal of the Association of Physicians of India 2000;48(4):376-380.

OBJECTIVETo study the spectrum of neurobrucellosis in a prospective study at Bikaner which is supposed to be uncommon in India.METHODThis study was done on admitted patients of brucellosis from June 1996 to June 1999 in whom the diagnosis was done by history of exposure to animals, fever and arthralgia and demonstration of brucella antibody titres in serum 1:160. CSF examination was done in all the patients. All cases were treated by combination of doxycycline 100 mg twice daily, rifampicin 900 mg daily for 6-8 weeks and injection streptomycin 0.75 to 1 gm i.m. per day for initial 14 days. Detailed neurological examination and antibody titres of serum and CSF again measured at the end of treatment.RESULTSTwelve out of 92 patients revealed evidence of neurobrucellosis in which four cases were of meningoencephalitis, two cases of myelitis leading to spastic paraparesis, five cases of polyradiculoneuropathy and one case of polyneuroradiculomyeloencephalopathy. The treatment regimen used was associated with a high cure rate and significant reduction in antibody titres in serum and CSF.CONCLUSIONNeurobrucellosis is an uncommon but serious manifestation affecting central and peripheral nervous system. The clinical profile of the disease mimicks closely to commonly seen neurological infective diseases like tubercular meningitis, viral encephalitis, aseptic meningitis, cerebral malaria and viral encephalopathy. Serum and CSF testing for brucella antibody titre is an important test for the diagnosis. Blood culture is not an ideal test for neurobrucellosis because of low yield and longer time required for the diagnosis. High degree of suspicion is prudent for the diagnosis. High degree of cure rate can be achieved by treatment with present regimen in a disease which is otherwise having high mortality and morbidity.

1. **Second episode of tuberculosis in an HIV-infected child: relapse or reinfection?**
Schaaf H. S The Journal of infection 2000;41(1):100-103.

We report a case of an HIV-infected child with a second episode of tuberculosis 22 months after completing antituberculosis treatment. DNA fingerprinting of organisms from both episodes showed an identical strain of Mycobacterium tuberculosis. We believe this to be the first case of confirmed relapsed tuberculosis in an HIV-infected child, and suggest that a longer course of antituberculosis treatment be given to such children. ¿ 2000 The British Infection Society.

1. **[Isoniazid-induced hepatic failure. Report of a case].**
Pereira R. M Arquivos de gastroenterologia 2000;37(1):72-75.

Isoniazid and pyrazinamide are both well-known hepatotoxic drugs. When isoniazid is used, the hepatic lesion appears before than when pyrazinamide is used. This paper intends to relate a case of a 5-month-old patient who had lungs' and meningeal tuberculosis and who developed toxic hepatitis accomplished by hepatic failure while he was being treated with isoniazid, pyrazinamide and rifampicin. The clinic manifestations and the laboratory alterations were detected in the fifth day of treatment and the recovery was fast; and almost complete by the end of the first week, in which the use of isoniazid had been suspended. Although it was necessary to take the patient to the intensive care unit, he had a good recovery, without sequels.

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1. **[Repeated deterioration of tuberculous meningitis due to a reduction in the corticosteroid dosage during chemotherapy].**
Miyoshi Y. Rinsho shinkeigaku = Clinical neurology 2000;40(10):1018-1022.

A 17-year-old man with a high fever, confusion and neck stiffness was diagnosed to have tuberculous meningitis, and was immediately placed on prednisolone (40 mg/day) as well as standard antituberculosis drugs (isoniazid, rifampicin and pyrazinamide). The clinical symptoms improved rapidly and the number of cerebrospinal fluid(CSF) cells decreased from 1837/mm3 on admission to 76/mm3 on the 7th day. Thereafter the dosage of prednisolone was gradually reduced. As a result, however increased nuchal rigidity, papilloedema and an increase in the number of CSF cells of 934/mm3 were all observed on the 35th day. Prednisolone thus again administered at the original dosage and the patient quickly showed a clinical improvement. CSF cells decreased to 271/mm3 on the 70th day. When prednisolone was again tapered down, increased nuchal rigidity, abducent nerve palsy and papilloedema appeared again with a marked increase in the number of CSF cells of 1309/mm3 on the 91th day. Therefore, we continued to treat the patient with prednisolone, in addition to the standard antituberculosis treatment, at a dose of 80 mg/day and tapered off very slowly over six months. This treatment resulted in a marked recovery with no recurrence. In this case, prednisolone was indispensable for treating tuberculous meningitis in combination with appropriate antituberculosis drugs, though the role of corticosteroids has remained controversial over the years. This case might be an example of paradoxical progression in tuberculous meningitis.

1. **Diagnosis and treatment of complicated tubercular meningitis**
Kelly J.J. Pharmacotherapy 1999;19(10):1167-1172.

A 41-year-old woman was seen in no acute distress with an infected ventriculoperitoneal shunt. She underwent several revisions of the shunt but was readmitted to the hospital with nausea, vomiting, and neurologic sequelae. Results of spinal fluid analysis were white blood cells 68/mm<sup>3</sup> (25% neutrophils), glucose less than 20 mg/dl, and protein 513 mg/dl. Cerebrospinal fluid, aerobic and anaerobic, and blood cultures were negative. Three weeks later the patient suffered a seizure and was prescribed antitubercular agents for a presumed diagnosis of tubercular meningitis. One week later, chest wound culture from her first visit suggested Mycobacterium tuberculosis, which was confirmed by DNA probe; cerebrospinal fluid culture eventually grew the organism. The patient fared well once she received antituberculosis agents. The time between first contact and treatment in the hospital delayed therapy.

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1. **Medical therapy of bone and joint tuberculosis in 1998.**
Pertuiset E. Revue du rhumatisme (English ed.) 1999;66(3):152-157.

Some measure of agreement and no little debate continue to surround the management of bone and joint tuberculosis. There is a consensus that the first phase of antituberculous chemotherapy should consist of three drugs (isoniazid, rifampin, and pyrazinamide) or four drugs (plus ethambutol) given for two to three months. When neither resistance nor side effects occur, isoniazid and rifampin should be continued as maintenance therapy. Patient compliance is well-recognized as requiring special attention because of its large impact on treatment outcomes. Provided strict patient selection criteria and close medical supervision are used, spinal cord compression can be treated nonsurgically with four antituberculous drugs, immobilization and, in many cases, a glucocorticoid. In spinal tuberculosis without neurological signs, immobilization is not always necessary, except when the cervical spine is involved. The optimal duration of antituberculous chemotherapy required for complete recovery of bone and joint tuberculosis is still debated. Twelve months is the duration currently recommended by most experts. Shorter durations, of six to nine months, have been advocated in adults. A critical analysis of the literature shows that proof is still lacking of the equivalence between six- to nine-month and 12- to 18-month treatments. In particular, trials conducted under the aegis of the Medical Research Council of the United Kingdom failed to resolve this issue because of methodological inadequacies regarding sample size and statistical analysis. The large sample size and long follow-up needed to obtain conclusive data would probably require a multicenter international study.

1. **Self-assessment questions**
Griffiths C. Current Paediatrics 1999;9(3):202-204.

1. **Tuberculosis of the central nervous system**
Garg R.K. Postgraduate Medical Journal 1999;75(881):133-140.

Tuberculous involvement of the brain and spinal cord are common neurological disorders in developing countries and have eloping recently shown a resurgence in developed ones. Tuberculous meningitis is an important manifestation and is associated with high morbidity and mortality. Diagnosis is based on features, cerebrospinal changes, and imaging characteristics. Bacteriological confirmation is not possible in all cases as serological tests do not have sufficient sensitivity and specificity. The polymerase chain reaction shows promise for the future. Appropriate chemotherapeutic agents should be administered as early as possible, although there is no unanimity concerning chemotherapeutic regimens or optimal duration of treatment. The patient's clinical stage at presentation is the most important prognostic factor. The role of corticosteroids is controversial but they should be administered to all patients presenting in stage III. Surgical procedures are directed at management of the hydrocephalus. Focal lesions, intracranial tuberculomas, and tuberculous abscesses, are usually located in cerebral or cerebellar hemispheres, uncommonly in brainstem and very rarely in spinal cord. They do not usually require surgical intervention and respond well to antituberculous treatment, along with corticosteroids.

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1. **A case of tuberculous meningitis with elevated activity of adenosine deaminase in cerebrospinal fluid in the early stage**
Saito K. Journal of Nara Medical Association 1998;49(1):34-38.

We report a case of tuberculous meningitis in a patient who was diagnosed with elevated activity of adenosine deaminase (ADA) in the cerebrospinal fluid (CSF) in the early stage of the disease. The patient was a 25-year-old female who was admitted to our hospital on Dec 10, 1996 because of fever, nausea, and headache. Tuberculous meningitis was strongly suspected based on clinical findings (including nuchal rigidity and decreased deep tendon reflexes in the lower extremities) and CSF findings (initial pressure 280 mmH<sub>2</sub>O, cell count 493/mul, protein 116 mg/dl, glucose 41 mg/dl, tryptophan reaction positive). Isoniazid, streptomycin, and rifampicin were administered. During treatment, no bacteria, fungi, or mycobacteria were detected in the CSF by both smear and culture examination. No mycobacterium tuberculosis RNA was detected using the Gen-Probe(TM) Amplified Mycobacterium Tuberculosis Direct Test. However, the patient was diagnosed as having tuberculous meningitis based on the increased activity of ADA (9.9 IU/l) in the CSF in the early stage of the disease and she recovered completely. Thus, measurement of ADA in the CSF is a useful tool for early diagnosis and follow-up of tuberculous meningitis.

1. **A combination of thalidomide plus antibiotics protects rabbits from mycobacterial meningitis-Associated death**
Tsenova L. Journal of Infectious Diseases 1998;177(6):1563-1572.

Tuberculous meningitis (TBM) is a devastating form of tuberculosis that occurs predominantly in children and in immunocompromised adults. To study the pathogenesis of TBM, a rabbit model of acute mycobacterial central nervous system infection was set up (8-day study). Inoculation of live Mycobacterium bovis Ravenel intracisternally induced leukocytosis (predominantly mononuclear cells), high protein levels, and release of tumor necrosis factor-alpha (TNF-alpha) into the cerebrospinal fluid within 1 day. Histologically, severe meningitis with thickening of the leptomeninges, prominent vasculitis, and encephalitis was apparent, and mortality was 75% by day 8. In animals treated with antituberculous antibiotics only, the inflammation and lesions of the brain persisted despite a decrease in mycobacteria; 50% of the rabbits died. When thalidomide treatment was combined with antibiotics, there was a marked reduction in TNF-alpha levels, leukocytosis, and brain pathology. With this combination treatment, 100% of the infected rabbits survived, suggesting a potential clinical use for thalidomide in TBM.

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1. **Candidal meningitis in HIV-infected patients**
Casado J.L. AIDS Patient Care and STDs 1998;12(9):681-686.

Candida meningitis is considered a rare event in HIV-infected patients, and little is known about risk factors, clinical presentation, therapy of choice, or outcome in this population. In a review of 14 cases, we observed a low frequency of the disease, a strong association to other well-known risk factors for systemic candidiasis, such as intravenous drug use, and a chronic course and clinical features that mimic those of cryptococcal or tuberculous meningitis. Although the role of fluconazole treatment remains to be defined, the combination of amphotericin B with flucytosine offers a survival rate similar to non-HIV-infected patients, In addition, the use of suppressive therapy with fluconazole for a prolonged period after clinical improvement seems recommendable.

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1. **Central nervous system tuberculosis after resolution of miliary tuberculosis.**
Chang A. B The Pediatric infectious disease journal 1998;17(6):519-523.

1. **Drug-resistant tuberculosis of the brain in a two-year-old child.**
Mehta J. B Tennessee medicine : journal of the Tennessee Medical Association 1998;91(7):285-287.

1. **Intensive short course chemotherapy in the management of tuberculous meningitis.**
Donald P. R The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease 1998;2(9):704-711.

SETTINGShort course chemotherapy for tuberculous meningitis (TBM) is advocated by several groups, but relatively few children have been so treated and followed up.METHODSA prospective, observational study of isoniazid (INH), rifampicin (RMP) and ethionamide (ETH) in a dosage of 20 mg/kg, and pyrazinamide (PZA) 40 mg/kg, all given once daily in hospital for 6 months. Surviving children were followed up for a year after discharge.RESULTSNinety five children, 39 (41%) at stage III, 52 (55%) at stage II and 4 (4%) at stage I TBM were studied. Ten (26%) at stage III and 3 (6%) at stage II died before completion of therapy. Five surviving children (6%) moved on discharge and were untraceable; seven children (9%) were lost during follow up and three were inadvertently restarted on antituberculosis therapy. Two children with severe stage III disease died after discharge. One child experienced a probable disease recrudescence 1 month after discharge. Eighteen children (20%) developed a mildly elevated serum bilirubin concentration during the first month of treatment. In five of these children INH, RMP, ETH and PZA were stopped and streptomycin (SM) and ethambutol substituted. In all cases the original treatment was restarted without incident. One child developed overt jaundice after 5 months of treatment due to hepatitis A infection.CONCLUSIONSOur experience suggests that young children with TBM can be safely treated for 6 months with high doses of antituberculosis agents without overt hepatotoxicity and with a low risk of relapse.

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1. **Treatment of pulmonary tuberculosis.**
van Loenhout-Rooyackers J. H The Netherlands journal of medicine 1998;53(1):7-14.

Recently the duration of treatment for pulmonary tuberculosis in The Netherlands was shortened from nine to six months. A six months regimen containing isoniazid (H), rifampicin (R) and pyrazinamid (Z) daily for two months, followed by H and R daily for another four months (2HRZ/2HR) has been proven effective for the treatment of pulmonary tuberculosis, provided the cause is a fully susceptible strain of M. tuberculosis. Worldwide there is an increase in drug-resistant tuberculosis. Since at the start of treatment susceptibility tests often are not available, a fourth drug must be added in the intensive phase. Ethambutol is the drug preferred. This means that one always starts with 4 drugs unless the patient is a contact of an index-case with proven susceptibility and one is sure that he will be compliant or the patient is infected in the past before 1940, he received never tuberculostatic drugs and one is sure that there is no exogenous reinfection. If the patient has been treated previously and anti-tuberculosis drug resistance is likely, treatment regimens should contain at least two drugs with which he has not been treated before, while a fifth drug routinely must be added in the intensive phase. Amikacin is preferred, since there is no cross-resistance to streptomycin. Consensus on the duration of treatment for extra-pulmonary tuberculosis has not yet been reached, but basically the principles for treatment are the same. This is also true for HIV infected tuberculosis patients. In some serious clinical situations (meningitis, miliary, spine tb) duration of treatment still is 9-12 months. Early involvement of the public health nurse of the municipal health department (GGD) is necessary to ensure patient compliance and treatment supervision.

1. **Cerebral infections in AIDS: Mycobacterial and other bacterial infections**
McArthur J.C. Infections in Medicine 1997;14(2):162-168.

Bacterial infections, including mycobacterial infections, must be part of the differential diagnosis of CNS infections in patients with AIDS. TB of the CNS is common in HIV-infected patients. Ring-enhancing lesions that do not respond to anti-Toxoplasma therapy are suggestive of CNS TB, especially in the presence of pulmonary TB. Mycobacterium avium-intracellulare, Nocardia, Listeria, and Clostridia are rare causes of CNS infection in patients with AIDS.

1. **Mixed meningococcal and tuberculous meningitis**
Yeh T.-H. Journal of the Formosan Medical Association 1997;96(6):461-464.

Meningococcal meningitis is one of the most common bacterial infections of the meninges worldwide, and tuberculous infection is the most common cause of chronic meningitis in Taiwan. However, mixed meningococcal and tuberculous meningitis is rare. We describe a 27-year-old woman with a case of culture- proven meningococcal and tuberculous meningitis verified by polymerase chain reaction on a cerebrospinal fluid specimen. The patient was initially treated with intravenous antibiotics including penicillin G and chloramphenicol. Though the patient responded well to therapy initially, her subsequent clinical deterioration was finally controlled by long-term antituberculous medications.

1. **Cerebral tuberculosis presenting as complex febrile convulsions.**
Berger C. Neuropediatrics 1996;27(3):161-163.

Complex febrile convulsions were the initial clinical manifestation of miliary tuberculosis in a 4-year-old immigrant girl. The cerebral lesions were visible only after contrast-enhanced cranial computed tomography (CT) while native CT scan as well as cell count and glucose concentration in the cerebrospinal fluid were normal. Mycobacterium tuberculosis was cultured from gastric aspirate and liver biopsy tissue. Treatment with isoniazid and rifampin for 12 months, pyrazinamide for 9 months, and ethambutol for the initial 6 weeks resulted in resolution of the cerebral lesions but a retinal scar after granuloma formation in the right eye caused reduced visus. This case demonstrates the importance of thorough search for tuberculosis even in the absence of overt clinical pulmonary signs especially in high-risk individuals such as immigrants.

1. **Fataler Verlauf einer tuberkulosen MeningitisFatal course of a case of consumptive meningitis**
Hermann W. Intensivmedizin und Notfallmedizin 1996;33(5):339-344.

We report on a case of consumptive meningitis in which, owing to larvate clinical symptoms and the incorrect diagnosis of paraclinical results, tuberculostatic therapy was only commenced 4 weeks after admission - a delay which proved fatal for the 39-year-old patient. Diagnostic errors initially led to the assumption of reactive psychosis with the risk of suicide, followed by suspicion of a frontobasal meningioma and then cerebral organic psychosyndrome. The state of the cerebrospinal fluid induced by subacute lymphocytic serous meningitis failed to be recognized in time. Consequently, a fatal course developed, including necrosis of the stem ganglions and cerebellum, generalized cerebral edema and progressive mid-brain symptoms. The patient died 5 weeks after admission.

1. **Presumed ocular and central nervous system tuberculosis in a patient with the acquired immunodeficiency syndrome.**
Muccioli C. American journal of ophthalmology 1996;121(2):217-219.

PURPOSETo elucidate a case of tuberculous choroiditis in a patient with the acquired immunodeficiency syndrome (AIDS).METHODSWe treated a 35-year-old woman who had AIDS with neurologic involvement caused by Mycobacterium tuberculosis. She developed a yellow-white chorioretinal infiltrate with indistinct borders and mild vitreitis in the right eye, probably caused by this pathogen.RESULTSThe patient's visual acuity improved in the right eye with healing of the ocular lesion and her neurologic condition improved after specific therapy with isoniazid, rifampin, and ethambutol.CONCLUSIONTuberculosis must be considered in the differential diagnosis of posterior uveitis and choroiditis in AIDS patients.

1. **Seltene bakterielle Infektionskrankheiten des ZNSRare bacterial infectious diseases of the CNS**
Pfister H.W. Aktuelle Neurologie 1996;23(5):189-196.

Meningitis due to Listeria monocytogenes used to be considered a rare disease, accounting for 2% of bacterial meningitis in adults. Recently there have been some clinical reports on an increased incidence of Listeria meningitis. Thus, the initial empiric therapy for bacterial meningitis in the adult should cover Listeria monocytogenes, for example by initiating antibiotic therapy with a cephalosporin of the 3rd generation plus ampicillin. Mycoplasma pneumoniae, a common pathogen of atypical pneumonias, may cause a wide spectrum of neurological complications that can be observed in 1 of 1000 patients suffering from Mycoplasma pneumoniae infection. Preceding respiratory disease and detection of specific antibodies are useful diagnostic pointers. Early diagnosis of tuberculous meningitis, which may lead to considerable difficulties in differential diagnosis, has markedly improved due to the use of polymerase chain reaction to detect mycobacterial DNA in the cerebrospinal fluid. Recently, the aetiologic pathogen of another rare chronic granulomatous encephalitis, Whipple's disease of the central nervous system, was identified by means of polymerase chain reaction: this pathogen is an actinomycete termed Tropheryma whippelii. Finally, the clinical characteristics and therapeutic regimens in other actinomycetic diseases, such as nocardiosis and actinomycosis, as well as in neurobrucellosis are described.

1. **The management of mycobacterial infections in HIV seropositive individuals. Jefferiss Wing Therapeutics and Protocols Group.**
Fisher M. International journal of STD & AIDS 1996;7(4):244-.

1. **[Fulminant hepatitis during the therapy for tuberculous meningitis].**
Garavelli P. L Recenti progressi in medicina 1996;87(12):597-.

1. **[Treatment of the secondary hydrocephalus of tuberculous meningitis by lateral ventricular drainage and drug injection].**
Chen Y. Zhonghua jie he he hu xi za zhi = Zhonghua jiehe he huxi zazhi = Chinese journal of tuberculosis and respiratory diseases 1996;19(5):297-299.

OBJECTIVETo decrease intracranial pressure rapidly and cure the secondary hydrocephalus of tuberculous meningitis.METHODSEvery case was drained at the frontal horn of lateral ventricle of non-predominant cerebral hemisphere, injected the mixture of 100 mg isoniazid and 2 mg dexamethasone into the lateral ventricle through ventricular drainage tube once every two days or once every day in some severe cases.RESULTSThe high intracranial pressure of 23 cases suffered from tuberculous meningitis were immediately decreased to normal level. The symptoms of 8 cases complicated with brain hernia were quickly improved. The cerebrospinal fluid became normal within 2-4 weeks after lateral ventricular drug injection.CONCLUSIONSLateral ventricular drainage and drug injection can obtain good result and provide a new approach to treatment of secondary hydrocephalus cases suffered from tuberculous meningitis.

1. **A controlled clinical trial of short-course chemotherapy for tuberculoma of the brain.**
Rajeswari R. Tubercle and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease 1995;76(4):311-317.

OBJECTIVEThe efficacy of a short-course regimen in the treatment of brain tuberculoma and computerised tomography (CT) scan appearance before, during and after antituberculosis treatment was studied in a controlled clinical trial.DESIGNPatients aged over 5 years with tuberculoma of the brain diagnosed by CT scan were randomly allocated to one of the following 2 regimens: Regimen 1: rifampicin, isoniazid and pyrazinamide daily for an initial 3 months followed by rifampicin and isoniazid twice-weekly for 6 months. Regimen 2: rifampicin, isoniazid and pyrazinamide thrice-weekly for an initial 3 months followed by rifampicin and isoniazid twice-weekly for 6 months. The patients were followed intensively for 2 years from the start of treatment.RESULTSOf the 108 patients analysed (regimen 1: 56, regimen 2: 52), at the end of treatment clinical status was normal in 91% in regimen 1 and 88% in regimen 2. Of the 91 patients with scan assessments, CT scan lesions disappeared at 24 months in 77% of 47 patients in regimen 1 and 80% of 44 in regimen 2, and in both groups 88% of the patients were clinically normal. None had relapses requiring treatment.CONCLUSIONSShort-course regimens of 9 months' duration are effective in the treatment of tuberculoma of the brain; clinical recovery was faster than scan clearance.

1. **Central nervous system infections: The usual and the unusual**
Lipton J.D. Emergency Medicine Clinics of North America 1995;13(2):417-443.

The emergency physician must have an intentional approach to the child suspected of having meningitis. Emerging diagnostic tools and therapies, including the use of corticosteroids, are discussed. In addition, CNS infections that are less commonly seen are reviewed, including tuberculous meningitis and herpes simplex virus encephalitis.

1. **Isoniazid elimination kinetics in children with protein-energy malnutrition treated for tuberculous meningitis with a four-component antimicrobial regimen.**
Seifart H. I Annals of tropical paediatrics 1995;15(3):249-254.

The impact of changing environmental factors--disease, nutrition and a high-dose multi-drug treatment regimen--on isoniazid (INH) elimination kinetics in children of both sexes and various ages was investigated. Thirteen children (mean age 2.3 years), hospitalized for the treatment of tuberculous meningitis, participated in the trial. Although all the children had protein-energy malnutrition, none had marasmus or kwashiorkor. After an oral dose of 20 mg/kg of INH, the concentrations in plasma were determined by the liquid chromatographic method of Lacroix et al. The 2-hour post-dose isoniazid concentration, the apparent first-order elimination rate constant and the corresponding INH half-life were determined in each child on two occasions 6 months apart. All comparisons were tested for significance using the Wilcoxon matched-pair signed-ranks test. There was no significant difference in any of the pharmacokinetic parameters of INH in our patients evaluated at the extremes of the 6-month term of treatment. It was apparent that changing conditions of disease and nutrition and a high-dosage, multi-component antimicrobial agent regimen over a 6-month period of treatment did not significantly influence INH elimination parameters. The trend evident in the pharmacokinetic profile of isoniazid in our children supports a trimodal distribution of acetylator phenotypes.

1. **Presumed central nervous system Whipple's disease in a child: Case report**
Tan T.Q. Clinical Infectious Diseases 1995;20(4):883-889.

Whipple's disease is a rare, chronic, multisystem illness that is pathologically characterized by the accumulation of macrophages in the involved tissue that have a positive periodic acid-Schiff reaction. It is typically seen in middle-aged white men, and only four cases involving persons younger than 15 years of age have been reported. CNS Whipple's disease without intestinal manifestations is rare; only six cases have been reported in the literature, all involving adults. We report the case of a young boy with clinical, laboratory, radiographic, and pathological signs and symptoms consistent with CNS Whipple's disease who responded to therapy with trimethoprimsulfamethoxazole.

1. **Primary malignant melanoma of meninges: Atypical presentation of subacute meningitis**
Nicolaides P. Pediatric Neurology 1995;12(2):172-174.

Primary malignant melanoma of the meninges is described in a 5-year-old boy who presented with a 3-month history suggestive of subacute meningitis. Clinically the diagnosis of tuberculous meningitis was made and antituberculous treatment was begun. Despite this treatment, the patient's condition continued to deteriorate. Through cytologic examination of the cerebrospinal fluid malignant melanoma cells were identified, emphasizing the importance of this investigation in children with atypical meningitis. The diagnosis of malignant melanoma of the meninges was confirmed on brain biopsy.

1. **The impact of human immunodeficiency virus on response to treatment and recurrence rate in patients treated for tuberculosis: two-year follow-up of a cohort in Lusaka, Zambia.**
Elliott A. M The Journal of tropical medicine and hygiene 1995;98(1):9-21.

To examine the effect of HIV on response to treatment and recurrence rate in patients with tuberculosis (TB), we have followed 239 previously untreated, adult, TB patients in a prospective cohort study in Lusaka, Zambia. One hundred and seventy-four (73%) were HIV-1 antibody positive. Patients with sputum smear positive, miliary, or meningeal TB were prescribed 2 months daily streptomycin, thiacetazone, isoniazid, rifampicin, pyrazinamide followed by 6 months thiacetazone and isoniazid; others, 2 months streptomycin, thiacetazone and isoniazid followed by 10 months thiacetazone and isoniazid. Thirty-five per cent of HIV-positive (HIV+ve) and 9% of HIV-negative (HIV-ve) patients were known to have died before the scheduled end of treatment. Surviving HIV+ve patients showed weight gain and improvement in symptoms and laboratory and radiological findings similar to HIV-ve patients. The risk of cutaneous drug reaction was 17% (95% CI: 12-25%) in HIV+ve, and 4% (1-13%) in HIV-ve patients. Severe rashes were attributed to thiacetazone. Recurrence of active TB was examined among 64 HIV+ve and 37 HIV-ve patients who successfully completed treatment, with mean follow-up after the end of treatment of 13.5 and 16.8 months, respectively. The rate of recurrence was 22/100 person years (pyr) for HIV+ve patients and 6/100 pyr for HIV-ve patients, giving a recurrence rate ratio of 4.0 (95% CI 1.2-13.8, P = 0.03).

1. **Treatment of tuberculosis and tuberculosis infection in adults and children**
Bass Jr. J.B. Clinical Infectious Diseases 1995;21(1):9-27.

Treatment of Tuberculosis: 1. A 6-month regimen consisting of isoniazid, rifampin, and pyrazinamide given for 2 months followed by isoniazid and rifampin for 4 months is the preferred treatment for patients with fully susceptible organisms who adhere to treatment. Ethambutol (or streptomycin in children too young to be monitored for visual acuity) should be included in the initial regimen until the results of drug susceptibility studies are available, unless there is little possibility of drug resistance (i.e., there is less than 4% primary resistance to isoniazid in the community, and the patient has had no previous treatment with antituberculosis medications, is not from a country with a high prevalence of drug resistance, and has no known exposure to a drug-resistant case). This four-drug, 6-month regimen is effective even when the infecting organism is resistant to INH. This recommendation applies to both HIV-infected persons and those who are not infected with HIV. However, in the presence of HIV infection it is critically important to assess the clinical and bacteriologic response. If there is evidence of a slow or suboptimal response, therapy should be prolonged as judged on a case by case basis. 2. Alternatively, a 9-month regimen of isoniazid and rifampin is acceptable for persons who cannot or should not take pyrazinamide. Ethambutol (or streptomycin in children too young to be monitored for visual acuity) should also be included until the results of drug susceptibility studies are available, unless there is little possibility of drug resistance (see Section 1 above). If INH resistance is demonstrated, rifampin and ethambutol should be continued for a minimum of 12 months. 3. Consideration should be given to treating all patients with directly observed therapy (DOT). 4. Multiple-drug-resistant tuberculosis (i.e., resistance to at least isoniazid and rifampin) presents difficult treatment problems. Treatment must be individualized and based on susceptibility studies. In such cases, consultation with an expert in tuberculosis is recommended. 5. Children should be managed in essentially the same ways as adults using appropriately adjusted doses of the drugs. This document addresses specific important differences between the management of adults and children. 6. Extrapulmonary tuberculosis should be managed according to the principles and with the drug regimens outlined for pulmonary tuberculosis, except for children who have miliary tuberculosis, bone/joint tuberculosis, or tuberculous meningitis who should receive a minimum of 12 months of therapy. 7. A 4-month regimen of isoniazid and rifampin is acceptable therapy for adults who have active tuberculosis and who are sputum smear- and culture- negative, if there is little possibility of drug resistance (see Section 1 above). 8. The major determinant of the outcome of treatment is patient adherence to the drug regimen. Careful attention should be paid to measures designed to foster adherence and to ensure that patients take the drugs as prescribed. The use of fixed drug combinations may enhance patient adherence and may reduce the risk of inappropriate monotherapy, and it may prevent the development of secondary drag resistance. For this reason, the use of such fixed drug combinations is strongly encouraged in adults. Virtually all the treatment regimens may be given intermittently if directly observed, thus assuring adherence.

1. **Treatment of tuberculous meningitis in Turkey.**
Doğanay M. Scandinavian journal of infectious diseases 1995;27(2):135-138.

A prospective study was performed on 72 cases of tuberculous meningitis studying various treatments. 37 patients were treated with a combination of isoniazid, rifampicin, pyrazinamide and streptomycin for 2 months, followed by a combination of isoniazid and rifampicin for 6 months. 35 patients were treated with various combinations of antituberculous drugs for 12-16 months. Disappearance of symptoms took (mean) 17 days. Mean duration of therapy for the hospitalized patients was 36 +/- 4 days. Seven (9.7%) patients died, 5 in the short-course therapy group and 2 in the long-course therapy group. Sequelae persisted in 18 (31%) cases, 8 of which cases were in the short-course therapy group and 10 in the long-course therapy group. No relapse was observed in either of the groups.

1. **Bacterial meningitis in Swaziland: An 18 month prospective study of its impact**
Ford H. Journal of Epidemiology and Community Health 1994;48(3):276-280.

Study objective - To describe the epidemiology, clinical features, and outcome of bacterial meningitis in Swaziland. Design - Prospective study of patients diagnosed as having meningitis of non-viral aetiology during an 18 month period from February 1991 to July 1992. Setting - Four regional hospitals covering the population of the four districts in Swaziland. Subjects - All patients with non-viral meningitis admitted to hospital within the study period. Main results - Altogether 85 patients were reported to have bacterial meningitis: 48.3% were aged under 1 year. Causative organisms were identified in 60% of cases, and Streptococcus pneumoniae was found to be the commonest (49% of cases). Overall, case fatality was 38.8% for all age groups, and 62.5% (15 of 25) for adults. Neurological sequelae occurred in 22.4%. Three of the adult cases were HIV seropositive. Seizures, but not duration of symptoms before admission, were associated with a poor prognosis. There was a significant rise in incidence related to a period of drought. Fifteen patients were reported with tuberculous meningitis, of whom five were known to be HIV seropositive; the case fatality was 73.3%. Conclusions - The aetiology and age distribution of cases of meningitis differs greatly from that in developed countries. Rising HIV infection may have an important impact on the future incidence of meningitis. The high case mortality found should encourage efforts towards earlier diagnosis and treatment, and strengthens the need to develop appropriate vaccines.

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1. **Hydrazine production in children receiving isoniazid for the treatment of tuberculous meningitis.**
Donald P. R The Annals of pharmacotherapy 1994;28(12):1340-1343.

OBJECTIVETo study the generation of the hepatotoxin hydrazine in 32 malnourished children receiving isoniazid for the treatment of tuberculous meningitis.DESIGN AND SETTINGThis observational study was undertaken in the pediatric ward of a teaching hospital admitting children with advanced forms of tuberculous meningitis for treatment and management of complications.METHODSThirty-two children (mean age 2.28 years) receiving isoniazid 20 mg/kg/d were studied. Plasma isoniazid, acetylisoniazid, and hydrazine concentrations were determined by an HPLC method. Fourteen children were studied at weekly intervals for the first month of treatment and again after six months of therapy; 18 additional children were studied on one or more occasions during the first month of treatment only.RESULTSThe area under the curve for hydrazine two to five hours after the isoniazid dose correlated with the isoniazid elimination rate and with acetylisoniazid generation. Hydrazine production increased significantly during the first month of treatment, but decreased to approximate initial values at six months. No correlation was found between any clinical or biochemical indicator of liver dysfunction and hydrazine production.CONCLUSIONSHydrazine is formed in significant concentrations during the metabolism of isoniazid in young children. However, additional factors such as preexisting liver damage (e.g., from viral hepatitis) may be necessary for it to reach its toxic potential.

1. **MENINGITES INFECTIEUSES A LIQUIDE CLAIR ET MENINGITES PURULENTES DE L'ENFANTAseptic meningitis and bacterial meningitis in children**
Bourrillon A. Revue du Praticien 1994;44(9):1253-1261.

1. **Meningitis**
Lambert H.P. Journal of Neurology Neurosurgery and Psychiatry 1994;57(4):405-415.

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1. **Mycobacterial infection in renal transplant recipients**
Hall C.M. Chest 1994;106(2):435-439.

Study objective: To determine the prevalence and presentation of mycobacterial infection as well as the influence on outcome in graft function and patient survival in renal transplant recipients at our institution. Design: A retrospective review of case records of all renal transplant recipients from 1980 to 1992. Setting: Groote Schuur Hospital, a large teaching hospital and regional tertiary referral center in Cape Town, South Africa. Patients: During the period reviewed, 857 transplants were performed. The records of 487 patients who had remained in Cape Town were examined. Results: There were 22 cases of mycobacterial infection (21 confirmed or presumed Mycobacterium tuberculosis and 1 unidentified Mycobacterium other than tuberculosis). In seven cases, immunosuppression had been intensified within 3 months of diagnosis. The median time from transplantation to diagnosis was 14 months (range, 2 to 74). Chest radiograph findings included consolidation (14), miliary pattern (4), pleural effusion (3), tuberculoma (2), cavitation (2), and hilar lymphadenopathy (1). Diagnosis of tuberculosis was made on sputum smears (eight), pleural biopsy specimen (two), fine- needle aspiration (one), and fiberoptic bronchoscopy in ten cases (brushings, eight; transbronchial biopsy specimen, three). Extrapulmonary tuberculosis (in addition to pulmonary tuberculosis) occurred in five patients (tuberculous meningitis, one; renal tuberculosis, one: and disseminated infection, four). Five of the seven patients in whom immunosuppression had been intensified had concurrent infections; two of these died and the remainder returned to dialysis within 6 months. All but one patient received three antituberculosis drugs, including rifampin and isoniazid, for between 6 and 18 months. At the end of the period of review, 12 (59 percent) patients were alive, 10 with functioning grafts and 2 receiving dialysis. Four patients died while receiving antituberculosis treatment, but death was only directly related to tuberculosis in one case. Conclusions: Tuberculosis is an important infection in renal transplant recipients in Cape Town, but disseminated disease is less common than reported elsewhere.

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1. **Randomized controlled trial of dexamethasone in tuberculous meningitis**
Kumarvelu S. Tubercle and Lung Disease 1994;75(3):203-207.

Setting: The patients admitted to the Neurology ward of the All India Institute of Medical Sciences Hospital. Objective: To assess the role of dexamethasone as an adjunct to antimicrobial therapy in the treatment of tuberculous meningitis. Design: A randomised controlled trial of 47 patients was conducted over a 13-month period. 41 patients completed the trial. Patients were stratified into mild, moderate and severe groups and randomly allocated to steroid and non-steroid groups. All patients received a standardized antituberculosis drug regime. The end point was 3 months, or death if earlier. The evaluation at the end point included survival, resolution of symptoms, sequelae and activities of daily living. Results were analysed using the Wilcoxon rank sum test. Results: The patients in the dexamethasone group fared better. 75% of this group had mild sequelae as opposed to 62% of the control group. Amongst the survivors, those who received dexamethasone sensorium improved earlier, and there was greater improvement in mental function and daily activities. The difference, however, did not reach statistical significance. Conclusions: Dexamethasone appears useful as an adjunct in the treatment of tuberculous meningitis especially in patients who have severe disease. The results need confirmation by a larger trial.

1. **Tuberculous meningoencephalitis after cytomegalovirus infection in renal transplant recipients**
Papagianni A. Nephrology Dialysis Transplantation 1994;9(4):438-442.

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1. **Use of polymerase chain reaction for diagnosis of tuberculous meningitis**
Mancao M.Y. Pediatric Infectious Disease Journal 1994;13(2):154-156.

1. **[Tuberculous meningitis caused by resistant microorganisms. Therapeuticfailure in 2 patients with HIV infection and disseminated tuberculosis].**
Fortún J. Enfermedades infecciosas y microbiologia clinica 1994;12(3):150-153.

BACKGROUNDTuberculosis in HIV infected patients does not carry a worse therapeutic response rate. Treatment failure is usually due to incomplete schedule, with development of acquired resistance. Two patients with HIV infection and disseminated tuberculosis who developed fatal meningitis are presented.METHODSIn vitro studies of sensitivity to anti-tuberculous drugs were carried out, using the proportions method.RESULTSFollowing a good initial evolution, both patients were readmitted with tuberculous meningitis resistant to isoniazide in both and to rifampicin in one of the patients. In one patient, the original strain (which was sensitive) was available. In this patient, changes in the treatment were performed in the initial phase.CONCLUSIONSThe importance of anti-tuberculous multiple therapy, particularly in the initial phases, for HIV positive patients is crucial. The lengthen of admission when good patient's compliance is in question, but also to avoid, whenever possible, changes in treatment are important measures in this stage. Meningitis may occur as a form of therapeutic failure and its cure may be difficult if the strains are resistant.

1. **Acute hydrocephalus in stage III tuberculous meningitis**
Sarnaik A.P. International Pediatrics 1993;8(4):446-451.

We report on four children with stage III tuberculous Meningitis (TBM) who presented with clinical signs of life-threatening intracranial hypertension at admission. Computerized tomography scan of the head showed generalized ventriculomegaly in all. Emergent ventricular decompression in addition to mechanical hyperventilation and osmotherapy resulted in marked neurologic improvement within 24 hours. All patients survived with satisfactory cognitive and gross motor function on long term follow up. We conclude that the pessimistic prognosis of stage III TBM is not universally warranted. Aggressive management of reversible complications of TBM such as acute hydrocephalus and cerebral edema can decrease the morbidity and mortality traditionally associated with stage III TBM. Conversely, failure to recognize and treat these factors may result in neuronal injury that is potentially available.

1. **Cerebrospinal fluid drug concentrations and the treatment of tuberculous meningitis.**
Ellard G. A The American review of respiratory disease 1993;148(3):650-655.

Tuberculous meningitis is a very serious form of tuberculosis. In the absence of randomized controlled trials of alternative treatment regimens, its management depends on employing potent drugs that penetrate well into the cerebrospinal fluid (CSF). The penetration of isoniazid, rifampin, and streptomycin into the CSF of 27 Chinese patients was studied using fluorimetric and microbiologic procedures. Isoniazid rapidly diffused into the CSF, peak concentrations in excess of 3 mg/L, or over 30 times its minimal inhibitory concentration (MIC) against Mycobacterium tuberculosis being attained within 4 hr. In contrast, rifampin and streptomycin penetrated very slowly across the meninges, and CSF levels only slightly in excess of their MICs against M. tuberculosis were achieved. The penetration of the drugs into the CSF correlated poorly with differences in their partitioning between octanol/water and cyclohexane/water but could be predicted using a simple model based on their renal clearance rates and plasma protein binding. It is recommended that patients with tuberculous meningitis should be treated for at least 9 months with a combination of isoniazid, rifampin, and pyrazinamide, which may be supplemented in the first 2 mo with streptomycin.

1. **GENERALISIERTE NOKARDIOSE MIT MENINGOENZEPHALITIS BEI EINER NICHT-IMMUNSUPPRIMIERTEN PATIENTINGeneralized nocardiosis with meningoencephalitis in a patient who was not immunosuppressed**
Hannemann J. Deutsche Medizinische Wochenschrift 1993;118(36):1281-1286.

Four weeks after an attack of pneumonia of unknown aetiology a 40-year-old woman was hospitalized because of a nonpurulent, predominantly basal meningoenecephalitis and infratentorial abscesses. She had dysarthria, mild right-sided motor hemiparesis and central paresis affecting the 7th cranial nerve. An area of fluctuating resistance, about 3 cm in diameter, was noticed over the left thigh. Serology indicated inflammatory disease, but there was no immunodeficiency. The CSF showed lymphocytic pleocytosis with mild protein increase but no evidence of infective agent. As tubercular meningitis was suspeected she was treated with rifampicin (300 mg i.v. twice daily), isoniazid (300 mg i.v. once daily), streptomycin (800 mg i.m. once daily), cefotaxim (2.0 g i.v. three times daily), fluconazole (200 mg i.v. once daily) and dexamethasone (16-8-8 mg i.v.). She suddenly died two days after admission, probably as the result of central regulatory failure. Generalized nocardiosis involving lung, subcutaneous tissue and brain was revealed at autopsy. Although nocardiosis occurs predominantly in patients under immunosuppression, this infection should be considered in the differential diagnosis of treatment-resistant pneumonia and meningoencephalitis without obvious predisposition.

1. **Optochiasmatic tuberculoma causing progressive visual failure: when has medical treatment failed?**
Poon W.S. Postgraduate Medical Journal 1993;69(808):147-149.

A 5 year old girl with tuberculous meningitis developed progressive visual failure during in-patient anti-tuberculous chemotherapy due to an optochiasmatic tuberculoma. This was successfully managed by prolonged high-dose corticosteroids and continued anti-tuberculous therapy resulting in complete visual and psychosocial recovery.

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1. **RISE-resistant tuberculous meningitis in AIDS patient [7]**
Horn D.L. Lancet 1993;341(8838):177-178.

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1. **Serum concentrations of rifampicin and isoniazid in tuberculosis.**
Seth V. Indian pediatrics 1993;30(9):1091-1098.

Ninety-four patients, 1-13 years of age suffering from different types of tuberculosis were investigated for serum rifampicin (RIF) and isoniazid (INH) concentrations using microbiological and fluorimetric methods, respectively. Of these, 64 (68.1%) had pulmonary primary complex (PPC); 20 (21.3%) progressive primary disease (PPD) and 10 (10.6%) tuberculous meningitis (TBM). Patients with PPC, PPD and TBM were given two-drug (6HR), three drug (2HRZ, 4HR) and four drug (2SHRZ, 4HRE, 3HE) regimens, respectively. RIF and INH were administered in a dose of 12 and 10 mg/kg/day, respectively. After 10-12 days of continuous therapy, their serum concentrations were estimated at 0, 2, 4, 6, 8 hours for RIF and 0, 1, 3, 5, 7 hours for INH. For RIF, the time to achieve maximum concentrations (Tmax) was 2 hours, range of mean of maximum concentration (Cmax) 3.38 to 3.88 micrograms/ml, terminal half life elimination (T1/2) 3.03 to 3.81 hours and area under serum concentration curve (AUC) 0-8 hours 24.7 to 28.3 micrograms/ml hours in different forms of tuberculosis. INH had a Tmax of 1 h, Cmax 4.38 to 8.17 micrograms/ml, T1/2 4.0 to 4.98 hours and AUC 0-7 hours 34.1 to 57.5 micrograms/ml hours. The concentrations achieved at 7-8 hours with these dosages were much above those required for therapeutic efficacy (minimum inhibitory concentration), being 50 to 250 times for RIF and 35-60 times for INH. We recommend pharmacokinetic studies with lower doses of RIF and INH for less toxic, equally effective and cheaper antitubercular chemotherapy.

1. **Short course chemotherapy for tuberculosis in children.**
Padmini R. Journal of tropical pediatrics 1993;39(6):361-364.

In order to determine the efficacy of short course chemotherapy (SCC) for tuberculosis in children, 83 newly diagnosed cases in children < 12 years old were given SCC and were prospectively followed for 1-3 years. Seventy-one cases were treated for 6-9 months as they had mild to moderate involvement. Twelve cases were treated for 12 months as they had meningitis (7), disseminated tuberculosis (2), or miliary tuberculosis (3). The results showed that none of the children, at the end of follow up, showed evidence of active tuberculosis. All children tolerated the drugs well, with side effects noticed being mild, namely transient hepatitis (4), vomiting (1), and skin rash (1). It is suggested that SCC for 6-9 months using isoniazid (INH) and rifampicin along with other drugs when necessary is highly effective in most cases of tuberculosis in children and has several advantages over conventional chemotherapy of 18 months or longer duration.

1. **UBERWIEGEND SUBAKUT VERLAUFENDE ENTZUNDLICHE ERKRANKUNGEN DES ZNSSubacute inflammation of the CNS**
Bamborschke S. Aktuelle Neurologie 1993;20(3):89-95.

Subacute inflammatory diseases of the CNS develop within days or a few weeks and in uncomplicated cases the patients recover within a few months. Cerebrospinal fluid (CSF) cell counts are relatively low (usually less than 300 cells/mul) and cell differentiation may show a mixed polymorphonuclear/mononuclear or a uniform mononuclear picture. CSF levels of protein, glucose, and lactate differ in respect of aetiology. The most important diagnoses are tuberculous meningitis, actinmomycosis, leptospirosis, neuroborreliosis, multiple cerebral microabscesses, neurobrucellosis, inflammation induced by varicella-zoster-virus, and neurosarcoidosis. History, physical examination, neuroimaging and CSF findings may show typcial features but do not allow definite diagnosis. In spite of the fact that new diagnostic test e.g. the polymerase chain reaction (PCR) have facilitated the detection of the aetiologic agent in some diseases, therapeutic decisions have to be made prior to diagnosis in most cases. Therefore, we discuss clinical findings, diagnostic procedures and therapeutic regimens of the eight diseases mentioned above in respect to rational decision making and management.

1. **[Tuberculosis of the central nervous system: value of early polychemotherapy. Apropos of 2 cases].**
Mukendi Kavulu R. Pediatrie 1993;48(6):491-492.

1. **A correlative study of intrathecally injected isoniazid and dexamethasone in children with tuberculous meningitis**
Wu W.W. Medical Science Research 1992;20(3):101-102.

1. **Bacterial meningitis in children: Selected aspects**
Bell W.E. Pediatric Clinics of North America 1992;39(4):651-668.

Accumulating clinical experience has gradually outlined the epidemiology of acute bacterial meningitis, including the epidemic and the sporadic forms, the customary clinical signs related to different age groups and causative organisms, and methods of rapid diagnosis by laboratory examinations. Effective treatment, which continues to evolve, emerged in the 1940s with the development of antibacterial antimicrobials, first with the sulfonamides and then with the penicillins. The literature relative to these aspects of the disease has been abundant in the past few years. This article is directed to a variety of topics that have direct bearing on the disorder but are less often addressed to those who deal with infants and children.

1. **Cerebrospinal fluid isoniazid concentrations in children with tuberculous meningitis: the influence of dosage and acetylation status.**
Donald P. R Pediatrics 1992;89(2):247-250.

Cerebrospinal fluid (CSF) and plasma isoniazid (INH) concentrations were determined on 96 occasions in 38 children (median age 1.5 years) with tuberculous meningitis, and the effects of INH elimination status and test dosages of 10 mg/kg body weight and 20 mg/kg body weight was studied. Maximum cerebrospinal fluid INH concentrations were reached during the period 2 to 4 hours after dosing and cerebrospinal fluid and plasma INH concentrations did not differ significantly during this period. Cerebrospinal fluid INH concentrations following a dosage of 10 mg/kg (4.6 +/- 2.4 micrograms/mL) were, however, significantly lower than those following a dosage of 20 mg/kg (11.6 +/- 2.7 micrograms/mL). Cerebrospinal fluid INH concentrations in faster acetylators at a dosage of 10 mg/kg (3.2 +/- 1.1 micrograms/mL) were significantly lower than in slower acetylators (7.7 +/- 1.3 micrograms/mL), as was the case with a dosage of 20 mg/kg, where faster acetylators had cerebrospinal fluid INH concentrations of 10.5 +/- 2.5 micrograms/mL compared with 14.1 +/- 1.4 microgram/mL in slower acetylators. Following dosages of both 10 mg/kg and 20 mg/kg, INH concentrations in excess of the minimal inhibitory concentration for Mycobacterium tuberculosis persisted in the CSF 12 to 14 hours later. Despite the patients' being young and frequently malnourished, suffering from advanced forms of tuberculous meningitis, and receiving high dosages of INH, rifampicin, and pyrazinamide, none developed any clinical signs of hepatotoxicity and in only one child did the serum bilirubin level rise to 19 micrograms/mL.

1. **Factors in hydrazine formation from isoniazid by paediatric and adult tuberculosis patients.**
Gent W. L European journal of clinical pharmacology 1992;43(2):131-136.

An HPLC method is described for measurement of plasma hydrazine (Hz) concentrations (CHz) at the same time as isoniazid (INH) levels (CINH). Study has been made of CHz during 2-5 after dose in healthy adults (A, n = 34), in adult pulmonary TB patients (B, n = 18) and in paediatric tuberculous meningitis patients (C, n = 25). Although the population has about equal proportions of 'slow' (52%) and 'fast' acetylators, in none of the groups could a correlation be shown between CHz levels or rates of Hz accumulation and any measure of acetylator type. Consequently Hz must be derived both from INH and from its metabolites during the first hours post-dose. For group A and ca. 70% of groups B and C a constant and maximal fraction of dose (ca. 0.6% for adults and 0.4% for paediatric patients) appeared as Hz at 4-5 h. For group B patients small pre-dose concentrations increased with duration of treatment. Four patients in group B showed the highest levels of CHz and rates of Hz accumulation some three times greater than the rest; all four had been identified as alcoholics and one showed evidence of hepatotoxicity at CHz (5 h) = 1.3% of dose. Amongst group C (9/25) episodes of high CHz greater than 0.5% of dose occurred during the first weeks of treatment and one developed CHz ca. 100 ng/ml = 1.3% of dose coincidentally with indications of hepatic damage.

1. **Intensive short course chemotherapy for tuberculous meningitis.**
Jacobs R. F The Pediatric infectious disease journal 1992;11(3):194-198.

This nonrandomized, open clinical investigation of tuberculous meningitis evaluated 53 children with Stage I (n = 8), Stage II (n = 29) and Stage III (n = 16) disease. The overall mortality was 20.8% (11 of 53) with a rate of sequelae of 35.7% (15 of 42) in survivors reflecting the advanced stages of children at diagnosis. Various combinations of standard antituberculous drugs including isoniazid, rifampin, pyrazinamide, streptomycin and ethambutol were given. Three treatment durations used during various time periods were evaluated: 12, 9 and 6 months with only the 6-month regimen receiving pyrazinamide (PZA). This prospective evaluation demonstrated that: (1) severe disease at presentation is highly associated with early mortality (P less than 0.05), regardless of drug regimen; and (2) intensive short course chemotherapy (6 months) with PZA, regardless of stage of disease at presentation, is more efficacious than longer course therapy (9 or 12 months) without PZA in preventing total negative outcomes and sequelae (P less than 0.05). This study demonstrates that a 6-month regimen containing PZA can be used in treating children with tuberculous meningitis.

1. **Neurotuberculosis: A review**
Al-Deeb S.M. Clinical Neurology and Neurosurgery 1992;94:-.

Tuberculosis is still a major cause of serious illness in many parts of the world. CNS involvement has frequently been found secondary to tuberculosis elsewhere in the body, particularly the lungs. The disease manifests itself as meningitis, tuberculoma and/or spinal tuberculosis. The presence of tuberculosis elsewhere in the body favors the diagnosis although its absence does not exclude it. While tuberculous meningitis is a disease of childhood, tuberculomas and spinal tuberculosis are invariably an adult manifestation. The great majority of patients with neurotuberculosis are diagnosed and treated early because of characteristic clinical, imaging, and CSF findings. Clinical response to antituberculous therapy in all forms of neurotuberculosis is excellent if the diagnosis is made early before irreversible neurological deficit is established.

1. **[Acute rhinopharyngitis, acute interstitial pneumonia and parieto-frontal brain abscess with H. influenzae type B].**
Mihancea N. Pneumoftiziologia : revista Societatii Romane de Pneumoftiziologie 1992;41(1):56-57.

The paper deals with a parietal frontal cerebral abscess caused by HITB biotype I in a girl aged 8 months. First a meningitis is suspected, then a tuberculous meningitis unsuccessfully treated with ampicillin, biseptol, respectively INH, rifampicin, pyrazinamide, prednisone, phenobarbital and chloramphenicol. The patient died through a central respiratory standstill on the 17th day of disease. The anatomopathological examinations revealed a giant parietal frontal cerebral abscess. H.influenzae, (serum type B, biotype I) resistant to ampicillin, chloramphenicol, Kanamycin, rifampicin and tetracycline but sensitive to erythromycin and neomycin was also found. A pharyngeal infection with HITB was presumably the origin of the abscess.

1. **[Evaluation of the treatment of adult tuberculous meningitis].**
Yu B. Z Zhonghua jie he he hu xi za zhi = Zhonghua jiehe he huxi zazhi = Chinese journal of tuberculosis and respiratory diseases 1992;15(2):79-81.

Through analysis of the treatment in 205 patients of adult tuberculous meningitis, we considered: 1. effective and vigorous alleviation of high intracranial pressure in early stage, 2. appropriate dosage of corticosteroids and, 3. correct selection of antituberculous drugs was the mainstay for chemotherapy of tuberculous meningitis. The results were 82 patients (40.0%) were cured, 101 cases (49.3%) improved, 15 cases (7.3%) died and 7 cases (3.4%) had complications. 175 cases have been followed-up from two to five years, all of them are alive.

1. **A review of the treatment of bacterial meningitis**
Girgis N.I. Transactions of the Royal Society of Tropical Medicine and Hygiene 1991;85:1-3.

This is a review of our experience in the treatment of meningitis carried out at the Naval Medical Research Unit No. 3 (NAMRU-3), Cairo, Egypt since 1967. We have demonstrated that the serum and cerebrospinal fluid concentrations of ampicillin and its efficacy when used in the treatment of meningitis are comparable whether they are administered intravenously or intramuscularly. The third generation cephalosporin ceftriaxone was found to be very safe and effective when administered intramuscularly once a day in the treatment of the different types of acute bacterial meningitis. Aztreonam given intramuscularly was successful in the treatment of Gram-negative meningitis caused by multi-resistant organisms. The fatality rates and morbidity were significantly reduced in patients with meningitis when dexamethasone was given in conjunction with antibacterial chemotherapy.

1. **Antibiotic treatment of community acquired bacterial meningitis**
Overturf G.D. Transactions of the Royal Society of Tropical Medicine and Hygiene 1991;85:9-16.

Community acquired meningitis is predominantly caused by three agents: Haemophilus influenzae, Streptococcus pneumoniae and Neisseria meningitidis. Four physical properties of available drugs - molecular size, protein binding, lipid solubility and ionization - affect drug entry to the central nervous system (CNS). These factors, coupled with acute changes in bloodbrain barriers and intrinsic bactericidal activity, have a bearing on the success of treatment with all agents. Third generation cephalosporins have largely supplanted older regimens due to their intrinsic qualities of greater bactericidal activity, optimal cerebrospinal fluid pharmacokinetics, and low toxicity. The pharmacological principles of treatment of CNS bacterial infections, pharmacology of available drugs, and current treatment recommendations are reviewed.

1. **Effect of steroids on cerebrospinal fluid penetration of antituberculous drugs in tuberculous meningitis**
Kaojarern S. Clinical Pharmacology and Therapeutics 1991;49(1):6-12.

Sixteen patients treated with oral isoniazid, pyrazinamide, rifampin, and intramuscular streptomycin for tuberculous meningitis were studied. The concentrations of isoniazid, pyrazinamide, rifampin, and streptomycin in cerebrospinal fluid (CSF) obtained 3 hours after administration were 2.40, 34.78, 0.29, and 3.78 mug/ml, respectively. The CSF concentrations of isoniazid and pyrazinamide were well above the minimum inhibitory concentration for Mycobacterium tuberculosis. Concentrations of rifampin and streptomycin were above the minimal inhibitory concentration initially but declined below the minimal inhibitory concentration at late times. The CSF penetration of isoniazid, pyrazinamide, rifampin, and streptomycin was about 89%, 91%, 5%, and 20%, respectively. In eight patients who received antituberculous drugs in combination with steroids, the mean CSF and serum concentrations, as well as CSF/serum ratios at various intervals of treatment, were not statistically different (p &gt; 0.05) from those of the eight patients who did not receive steroids.

1. **Role of surgery in tuberculous mastoiditis**
Singh B. Journal of Laryngology and Otology 1991;105(11):907-915.

A study was undertaken in 43 patients to determine the role of surgery in tuberculous mastoiditis. Cortical mastoidectomy was performed on five patients (Group I). Incision and drainage of a post-auricular abscess, removal of sequestrum and meatoplasty in eight (Group II). Thirty patients had no ear surgery (Group III). Of the 17 patients with facial palsy, three were in Group I, two in Group II, 12 in Group III. The patients in all three groups were treated with anti-tuberculous drugs for a period of no less than six months. The average time taken for the otorrhoea to subside and granulation tissue to resolve completely was two months in all three groups. The facial nerve recovery in the non-operated ears (Group III) was 92 per cent and in the operated ears (Group I and II) 80 per cent. The conclusion is that chemotherapy is the management of choice in tuberculous mastoiditis. The only role of surgery is incision and drainage of a post-auricular abscess and removal of sequestrum if present.

1. **Brain stem tuberculoma in adult patients: diagnosis and treatment.**
Farrell V. J Surgical neurology 1990;34(6):383-389.

A consecutive series of six adult patients ranging in age from 29 to 53 years is presented. The clinical and radiological features in each patient are described. Attention is drawn to the features demonstrated on computed axial tomography. In only one patient, the first encountered, was surgical excision undertaken and histological verification obtained. One patient died before any form of treatment could be instituted. The remaining four patients were treated with antituberculous chemotherapy alone and their progress monitored by sequential computed tomography. The excellent response and good outcome in this conservatively treated group are documented.

1. **Short course chemotherapy for childhood tuberculosis.**
Biddulph J. The Pediatric infectious disease journal 1990;9(11):794-801.

A prospective study, with an attempted 24-month-post-treatment follow-up, of children with tuberculosis (TB) treated with short course chemotherapy (SCC) for 6 months was carried out because published experience of SCC in childhood TB was limited. All children in Port Moresby diagnosed as having TB between November, 1984, and November, 1986, entered the trial. Of the 639 children 165 (26%) were younger than 2 years old. Of these, 227 (35%) had extrapulmonary TB (peripheral lymph node, 110; central nervous system, 43; abdominal, 27; miliary, 16; bone and joint, 11; pleural, 11; polyserositis, 9). Clinical response to SCC was rapid. Adverse drug reactions occurred in 15 (2%), mainly to streptomycin. Twelve (2%) died, 38 (6%) transferred out and 145 (28% of the 518 who did not die, transfer or live too far from a treatment centre) defaulted. Three hundred seventy-three (58%) completed a 2-month course of daily rifampin, isoniazid, pyrazinamide and streptomycin followed by a 4-month course of twice weekly rifampin and isoniazid. A further 71 (11%) had their treatment modified because of their distance from a treatment center. Only 70 (19%) of the 373 children available for post-treatment follow-up attended the every-3-month follow-up visits for 24 months, although 223 (60%) attended one or more of the follow-up visits. Seven of the 373 children relapsed, mostly within 3 months. Five of these children had been irregular with their treatment. SCC for childhood TB is safe and effective for pulmonary and extrapulmonary disease.

1. **The blood/cerebrospinal fluid partitioning of pyrazinamide: a study during the course of treatment of tuberculous meningitis.**
Phuapradit P. Journal of neurology, neurosurgery, and psychiatry 1990;53(1):81-82.

Concentrations of pyrazinamide were measured in serum and cerebrospinal fluid (CSF) of 17 adult patients with tuberculous meningitis up to six months after starting treatment. Pyrazinamide penetrated excellently into the CSF and mean concentrations at various intervals up to six months of treatment were consistently above that required for inhibition of the growth of Mycobacterium tuberculosis. The blood/CSF partitioning of pyrazinamide does not change as the patients recover from the meningitis.

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1. **Tuberculous meningitis in a female patient on long-term corticosteroid therapy**
Van Schoorl J. Tijdschrift voor Geneeskunde 1990;46(23):1705-1708.

1. **Tuberculous meningitis. 23 cases from a 12-year period (1976-1987).**
Jensen T. H Danish medical bulletin 1990;37(5):459-462.

Twenty-three patients with tuberculous meningitis were reviewed to see whether clinical features or initial laboratory findings could discriminate between these patients and other patients with bacterial meningitis. Nineteen patients were Danes and four immigrants. Preexisting diseases were found in eight cases. Duration of symptoms could be related to neurological sequelae, but not to death. The initial clinical picture was indistinguishable from meningitis of other causes. Microscopy of the cerebrospinal fluid (CSF) was negative in all but two cases, where acid fast bacilli were found. CSF cytology and biochemistry could not discriminate from other causes bacteria of meningitis although CSF/blood glucose ratio in 56% was below 0.3. One of the most important pieces of information in establishing an early diagnosis in tuberculous meningitis is the anamnestic information, and therapy often has to be started without knowing the microbiological data.

1. **Internuclear ophthalmoplegia in tuberculous meningitis.**
Teoh R. Tubercle 1989;70(1):61-64.

Two patients with tuberculous meningitis and internuclear ophthalmoplegia are described. Despite treatment with anti-tuberculosis chemotherapy and corticosteroids, both patients died. In one case autopsy showed severe basal meningitis with diffuse brain stem infarction secondary to widespread vasculitis.

1. **Treatment of tuberculous meningitis in adults with a combination of isoniazid, rifampicin and streptomycin: a prospective study.**
Doğanay M. Scandinavian journal of infectious diseases 1989;21(1):81-85.

15 patients with tuberculous meningitis were treated with isoniazid, streptomycin and rifampicin and 14 with isoniazid, streptomycin and ethambutol for 12 months. Both groups received prednisolone at the beginning of treatment. The two groups were compared with regard to clinical improvement, presence of neurological sequelae and mortality. No difference in recovery rate between the groups was observed. 6 patients (21%) died (5 in group I and 1 in group II). Residual sequelae developed in 9 cases (5 in group I and 4 in group II; 31%). The difference between the groups was not significant. The regimen including rifampicin for tuberculous meningitis did not result in any superiority compared to standard therapy.

1. **Tuberculosis in children and its management.**
Abernathy R. S Seminars in respiratory infections 1989;4(3):232-242.

Children with tuberculosis (TB) in the United States are generally asymptomatic, 60% are under 5 years, 80% belong to racial/ethnic minorities or are foreign born, and most are diagnosed during the investigation of contacts of known cases of pulmonary TB. A presumptive diagnosis of primary TB is made on the basis of a positive tuberculin reaction and a characteristic chest roentgenogram, usually showing hilar adenopathy. Treatment may be with isoniazid (INH) and rifampin (RIF), largely twice weekly for 9 months, or INH, RIF, and pyrazinamide for 2 months followed for 4 months by INH and RIF. Four drugs are needed in cases of infection with drug-resistant organisms or in tuberculous meningitis. All therapy must be closely monitored for toxicity and compliance. In noncompliant families, all medication should be directly administered. This is now possible with short-course therapy, largely twice weekly. Preventive therapy for the tuberculin positive, but disease-free child, is provided more cost-efficiently with 6 months than with 12 months of treatment with INH; less than 6 months is not adequate. All tuberculin reactive children should receive INH for 6 months. More diligence in providing INH prophylaxis to adult reactors will decrease future infectious TB cases, and thus prevent transmission to other children.

1. **Tuberculous meningitis in children: treatment with isoniazid and rifampicin for twelve months.**
Visudhiphan P. The Journal of pediatrics 1989;114(5):875-879.

Patients with tuberculous meningitis were treated with isoniazid and rifampicin for 12 months. To evaluate the result of treatment, we studied the outcome of patients treated from January 1979 to December 1985. Of the 51 patients, 27 were female, and 5, 25, and 21 patients were in the first, second, and third stages of the disease, respectively. Increased intracranial pressure of greater than 200 mm H2O was observed in 42 patients. Three patients required ventriculostomy, and one of them needed ventriculoperitoneal shunting. Three patients died within the first week of admission, and four patients were lost to follow-up. Forty-four patients were followed for 1 1/2 to 7 years; 31 of them recovered completely. Thirteen patients recovered with neurologic sequelae, which included mental retardation, motor weakness, seizures, and hydrocephalus. No serious side effect of the drugs were observed except for transient elevation of liver enzyme activities in four patients. The combination of isoniazid and rifampicin for 1 year, with appropriate management of increased intracranial pressure, seemed to be safe and effective enough to be used as a routine treatment of tuberculous meningitis in areas where resistance to these drugs is uncommon.

1. **[Coma--accidental poisoning occurring in the isoniazid + rifampicin treatment of a 7-year-old child].**
Murgoci G. Revista de igiena, bacteriologie, virusologie, parazitologie, epidemiologie, pneumoftiziologie. Pneumoftiziologia 1989;38(2):149-156.

1. **[Tuberculous meningitis].**
Kaufman N. Harefuah 1989;116(4):194-195.

2 cases of tuberculous meningitis are presented, 1 in a 54-year-old woman who had immigrated to Israel from Turkey 36 years before, and the other in a 10-year-old girl who recently immigrated from Ethiopia. Since diagnosis is difficult and prompt antituberculous treatment is life-saving, treatment may be instituted before the bacteriological diagnosis is established. A short term treatment of 9 months and a combination of rifampicin and isoniazid were successful in our patients.

1. **A case of cerebral tuberculoma**
Matsumi N. IRYO - Japanese Journal of National Medical Services 1988;42(1):67-71.

1. **Therapeutic views on meningitis and encephalitis of adults**
Schulz K.-R. Zeitschrift fur Arztliche Fortbildung 1988;82(12):543-546.

1. **Cerebrospinal fluid and serum concentrations of rifampin in meningeal tuberculosis after intravenous administration.**
Mikhail I. A Chemioterapia : international journal of the Mediterranean Society of Chemotherapy 1987;6(2):-.

1. **LE MENINGITI BATTERICHEBacterial meningitis**
Di Nola F. Minerva Medica 1987;78(1):1-19.

After a presentation of purulent and liquoral bacterial meningitis with an examination of its pathogenesis, a personal case series is presented. Particular attention is paid to the liquoral transfer of antibiotics and it is considered that the treatment of purulent bacterial meningitis cannot be standardised. In contrast tubercular meningitis can be subjected to standardised treatment. Currently the results obtained in the treatment of purulent bacterial meningitis are less satisfactory than those obtained in tubercular meningitis though certainly better than in the recent past.

1. **Treatment of tuberculous meningitis: role of short-course chemotherapy.**
Phuapradit P. The Quarterly journal of medicine 1987;62(239):249-258.

Twenty-eight adult patients admitted consecutively with tuberculous meningitis were treated with pyrazinamide, isoniazid, rifampicin and streptomycin daily during the first two months, followed by isoniazid and rifampicin daily for seven months with intensive management of the complications during the active stage of the meningitis. Twenty-two patients completed the course of treatment and recovered with minimal morbidity in three patients. Two patients died in a vegetative state from other causes seven and nine months after the start of treatment. No evidence of recurrence of meningitis was observed in the 21 patients who were regularly observed for 12 to 29 months after completing treatment. Four patients dropped out during the early stage of treatment. Intensive chemotherapy of tuberculous meningitis with this regimen before the development of serious neurological damage can shorten the duration of treatment to nine months with a favourable outcome.

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1. **Chronic untreated tuberculous meningitis**
Traub M. Journal of Neurology 1986;233(4):254-256.

We describe a 34-year-old man who suffered from tuberculous meningitis for 2 years without receiving anti-tuberculous medication. Our case is compared with other forms of indolent or benign variants of the disease.

1. **CNS tuberculosis**
Sheller J.R. Neurologic Clinics 1986;4(1):143-158.

Tuberculous meningitis is a rare, treatable neurologic disorder, in which early recognition is paramount because outcome depends greatly on the speed with which therapy is initiated. Patients with meningitis and CSF findings of low glucose, elevated protein and pleocytosis with evidence of tuberculosis elsewhere in the body (chest radiographs, positive tuberculin skin test), or a history of exposure to tuberculosis should be treated immediately with antituberculous medication. When the diagnosis remains uncertain, serial examination of the CSF for tuberculous organisms will often yield positive results. The CT scan may show hydrocephalus, a basilar arachnoiditis, or intraparenchymal lesions: tuberculomas. Hydrocephalus may respond to early shunting. Tuberculomas are best treated medically. Therapy should include INH and rifampin; ethambutol and pyrazinamide are suggested for the first 2 months of therapy. Steroids may be useful in diminishing the inflammatory response when altered consciousness or focal neurologic signs are present.

1. **Effect of dose formulation on isoniazid absorption in two young children.**
Notterman D. A Pediatrics 1986;77(6):850-852.

In an 8-month-old infant with tuberculous meningitis treatment with isoniazid was unsuccessful and was associated with lower than expected plasma concentrations of isoniazid (measured concentration 0.1 microgram/mL). The infant had received isoniazid as a crushed tablet admixed with apple sauce. Oral administration of the parenteral solution of isoniazid (Nydrazid, Squibb) mixed in apple juice produced a higher isoniazid concentration (2.9 micrograms/mL) and the child improved clinically. Pharmacokinetic studies in two subjects were performed following intramuscular injection of isoniazid and oral administration of (1) an isoniazid tablet crushed and mixed with apple sauce, (2) parenteral isoniazid solution mixed with apple juice, and (3) a commercially available syrup containing isoniazid and pyridoxine (P-I-N Forte, Lannett). Of the three oral preparations, the syrup produced the highest peak concentrations (8.3 and 6.9 micrograms/mL). The crushed tablets in apple sauce produced the lowest peak concentrations (1.4 and 2.4 micrograms/mL). Administration of crushed isoniazid tablets with food may be associated with impaired gastrointestinal absorption, lower than expected isoniazid concentrations, and treatment failure.

1. **Meningitis associated with tuberculous arthritis of the knee**
Maier W.P. American Journal of Medicine 1986;80(1):151-153.

This case report describes two uncommon manifestations of tuberculosis, meningitis and arthritis, occurring in a patient without pulmonary disease. Difficulties in diagnosis and results of treatment are discussed.

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1. **MENINGITIS TUBERCULOSA BEIM KIND - EINST UND JETZTTuberculous meningitis in children - Past and at present**
Dietzsch H.-J. Zeitschrift fur Erkrankungen der Atmungsorgane 1986;167(1):175-179.

From the point of view of a clinical pediatrician a short survey of the incidence and the earlier and more recent results concerning treatment and prevention of this life threatening localisation of tuberculosis is given. Because of some peculiarities the last case treated in our clinic is reported in detail. Finally the importance of the differential diagnosis of tuberculous meningitis is discussed.

1. **Pyrazinamide in treatment of tuberculous meningitis.**
Pauranik A. Archives of neurology 1986;43(10):982-.

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1. **Serum streptomycin levels in tuberculous meningitis in an infant**
Kibirige M.S. Lancet 1986;1(8484):806-807.

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1. **Three chemotherapy studies of tuberculous meningitis in children.**
Ramachandran P. Tubercle 1986;67(1):17-29.

Chemotherapy studies were undertaken in 180 patients with tuberculous meningitis. They were treated for 12 months with 1 of 3 regimens: the first consisted of streptomycin, isoniazid and rifampicin daily for the first 2 months, followed by ethambutol plus isoniazid for 10 months; in the second, pyrazinamide was added for the first 2 months, and in the third, rifampicin was reduced to twice weekly in the first 2 months. Steroids were prescribed for all the patients in the initial weeks of treatment. Approximately 50% of the patients were aged less than 3 years. On admission, 13% of the patients were classified as stage I, 77% as stage II and 9% as stage III. Cerebrospinal fluid (CSF) culture results were available for all the 180 patients and M. tuberculosis was isolated in 59 (33%). CSF smear results for acid fast bacilli were available only for the 103 patients admitted to the second and the third studies, and of these in 60 (58%) the CSF was positive either by smear or culture. The response to therapy was similar in the 3 studies. Despite administration of rifampicin for 2 months, the mortality was high. In all, 27% of the patients died of tuberculous meningitis, 39% had neurological sequelae and 34% recovered completely. There was a strong association between the stage on admission and the mortality rate, the deaths being highest in stage III. In the first study, when isoniazid was prescribed daily in a dosage of 20 mg/kg, 39% of the patients developed jaundice; however, when the dosage was reduced to 12 mg/kg, the incidence fell to 16%. In the third study, where rifampicin was administered twice a week, the incidence of jaundice was much lower (5%).

1. **A case of miliary tuberculosis with nodular dissemination to brain demonstrated by computed tomography**
Gemma H. Kekkaku 1985;60(8):455-459.

A case of miliary tuberculosis with tuberculous meningitis is reported. The computed tomography of the brain demonstrated spread of small nodular shadows in the brain. At the beginning the small nodular shadows increased both in number and size, which disappeared after six months combination treatment of anti-tuberculous drugs and corticosteroid hormone. These results suggest that the tuberculous miliary spread to brain was demonstrated by the computed tomography with advanced resolving power.

1. **A patient with tuberculous meningitis and a syndrome of inappropriate secretion of antidiuretic hormone**
Mulder H. Netherlands Journal of Medicine 1985;28(11):502-504.

A 72-year-old woman suffering from an extrapulmonary form of tuberculosis is described. In a rather bizarre presentation she showed the clinical picture and biochemical hallmarks of the syndrome of inappropriate secretion of antidiuretic hormone.

1. **Adult tuberculous meningitis: comparative study of different chemotherapeutic regimens.**
Acharya V. N The Journal of the Association of Physicians of India 1985;33(9):583-585.

1. **MANEJO MEDICO DE LA HIDROCEFALIA TUBERCULOSAMedical management of tuberculosis hydrocephalus**
Alarcon Egas F. Archivos de Neurobiologia 1985;48(3):133-136.

1. **MENINGITE TUBERCULEUSE. APPORT DE LA TOMODENSITOMETRIE AU DIAGNOSTIC ET AU PRONOSTICTuberculous meningitis. Contribution of computerized tomography to its diagnosis and prognosis**
Bonafe A. Journal of Neuroradiology 1985;12(4):302-316.

In a series of 36 patients with confirmed tuberculous meningitis, twelve (2 children, 10 adults) developed neurological complications. In 11 of these computerized tomography (CT) provided evidence of basilar arachnoiditis by showing blockade of the suprasellar cisterns. The meningeal exudate appears one month on average the clinical onset of meningitis. It is not influenced by antituberculous treatment of by systemic corticosteroid therapy prescribed from the start. Severe forms of basilar meningitis are complicated with disorders of cerebrospinal fluid (CSF) circulation, vascular lesions and tuberculomas. Hydrocephalus may be the first clinical manifestation and precede by several weeks the obliteration of basilar cisterns demonstrated by CT. Angiitis predominantly affects the territories of perforating arteries; it is reflected by lacunae in the basal ganglia and is often asymptomatic. Agiitis of medium caliber vessels results in sudden deficit symdrome. Tuberculomas that develop during treatment of tuberculous meningitis are located in the subarachnoid spaces and have no specific clinical symptoms. Their course towards regression, with or without intercurrent phases of activity, can be followed by CT.

1. **OSSERVAZIONI SU 78 CASI DI MENINGITE TUBERCOLARE: ASPETTI CLINICI, PROGNOSTICI E TERAPEUTICIRemarks on 78 cases of tubercular meningitis. Clinical, prognostical and therapeutical aspects**
Ciammarughi R. Giornale di Malattie Infettive e Parassitarie 1985;37(11):1078-1087.

1. **Tuberculous meningitis**
Molavi A. Medical Clinics of North America 1985;69(2):315-331.

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1. **[Evaluation of rifampicin-isoniazid treatment in tuberculous meningitis].**
Hermida-Escobedo C. Revista latinoamericana de microbiologia 1985;27(4):277-281.

1. **Aging and tuberculosis.**
Nagami P. Gerontology 1984;30(5):308-315.

In the United States, an increasing proportion of all forms of reactivation tuberculosis occurs in patients over the age of 60 years. Atypical presentations and presence of chronic illness obscure the diagnosis of tuberculosis in the elderly. Prompt diagnosis requires a high index of suspicion and aggressive procedures for diagnostic microbiology. Short-course (9 months) chemotherapy with isoniazid and rifampin is the treatment of choice for elderly patients with uncomplicated pulmonary tuberculosis. Isoniazid chemoprophylaxis is recommended for selected elderly patients.

1. **Rifampicin in tuberculous meningitis: a retrospective assessment.**
Latorre P. European journal of clinical pharmacology 1984;26(5):583-586.

To shed some light on the potential value of rifampicin in the treatment of tuberculous meningitis (TBM) in adults, a retrospective analysis has been made of 143 medical records from 4 hospitals for the period 1967-80. Treatment of TBM with rifampicin and other antituberculous drugs in combination (Group B) was compared to other regimes which did not include rifampicin (Group A). There were 64 patients in Group B and 79 in Group A. The two groups of patients did not differ significantly in their prognostic characteristics. The total mortality was 14.7%: it was higher among patients not treated with rifampicin (24%; Group A) than amongst those given rifampicin (3.1%; Group B; chi 2 = 10.74; p less than 0.005). The difference was also statistically significant (chi 2 = 6.88; p less than 0.01) if patients who died during the first 48 h after the institution of treatment were excluded. No significant difference in mortality rate was found when patients treated with rifampicin plus isoniazid (INH) 8-10 mg/kg (1 death out of 41 patients) were compared to patients treated with INH 15 mg/kg (2 deaths out of 20 patients). Neurological sequelae recorded during a 6 month follow-up period were more severe among patients not treated with rifampicin.

1. **Tuberculous meningitis in the elderly**
Dixon P.E. Postgraduate Medical Journal 1984;60(707):586-588.

Six cases of tuberculous meningitis, all occurring in patients over the age of 65, are described. All patients presented with an acute illness, primarily with a confusional state. Headache was a symptom in only two patients and the cases were not confined to ethnic minority groups. The mortality was 50%.

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1. **The use of dexamethasone in preventing ocular complications in tuberculous meningitis.**
Girgis N. I Transactions of the Royal Society of Tropical Medicine and Hygiene 1983;77(5):658-659.

Twenty-seven patients with tuberculous meningitis (TBM) were treated with ethambutol, isonicotinic acid hydrazide, streptomycin and dexamethasone and 28 were treated with triple anti-tuberculous drugs only. Only two of the patients to whom steroids were given developed ocular complications as compared to seven of those not receiving dexamethasone. High dose dexamethasone apparently prevents optic atrophy in TBM. Controlled double-blind studies with and without dexamethasone are needed to confirm this postulation.

1. **[Tuberculous meningitis--case report and therapeutic schedule].**
Elgefors B. Lakartidningen 1983;80(19):2027-2030.

1. **Brain-stem tuberculoma: an unusual presentation.**
Mahanta A. Journal of neurology 1982;227(4):249-253.

1. **[Treatment of tuberculous meningitis in adults: current trends and problems].**
Gallofre L.ópez M. Revista clinica espanola 1982;166(6):317-319.

1. **Intraventricular administration of rifampin for tuberculous meningitis.**
Dajez P. Journal of neurology 1981;225(2):153-156.

A case of tuberculous meningitis associated with cerebral tuberculomas, and resistant to antituberculous therapy is reported. Repeated injections of rifampin, administered through an intraventricular Ommaya drain, provided an effective control of the meningeal infection.

1. **Plasma concentrations of isoniazid in children with tuberculous infections.**
Olson W. A Pediatrics 1981;67(6):876-878.

Six children with tuberculous infection were given their daily prescribed doses of isoniazid by the oral and the intramuscular route on different days. The plasma concentrations reached after both routes of administration were nearly equivalent. The plasma half-life of isoniazid ranged from 1.6 to 4.8 hours. The observed plasma concentrations in these children were higher than those reported in many adults. This difference is due to the larger doses of isoniazid prescribed for children.

1. **Rimactan parenteral formulation in clinical use**
Kissling M. Journal of International Medical Research 1981;9(6):459-469.

One hundred and forty-nine mainly critically ill or comatose patients or patients with problems of gastro-intestinal tolerability and/or absorption have been treated during the last few years with a parenteral formulation of rifampicin made available for release in special cases, on humanitarian grounds. The cases reported include ninety-seven tuberculous patients (eighteen of whom were suffering from tubercular meningitis) and fifty-two patients suffering from non-tuberculous infections, including twenty-two cases of sepsis (fifteen due to staphylococci), four cases of bacterial meningitis and four cases of Legionnaires' disease. Rifampicin was administered in each case, together with at least one other suitable antibacterial agent, mainly by intravenous bolus injection (seventy-four cases) or intravenous drip infusion (forty-four cases), at daily doses ranging from 150 to 1800 mg. The duration of treatment ranged from 1 to 113 days. Data allowing an assessment of effectiveness were made available for sixty-eight tuberculous patients, sixty-three of which (92.6%) showed favourable results, and for twenty-seven patients with non-tuberculous infections, nineteen of which (70.4%) had a favourable outcome. Especially favourable were the results in the cases of staphylococcal sepsis (78.6% of clinical and/or bacteriological cures). Tolerability was good in most cases. Only fourteen of the 149 patients showed signs of local intolerability (thrombo-phlebitis), almost always occurring in patients treated for over 60 days. Fifteen patients (10%) complained of systemic unwanted effects, the relationship of which to the treatment was not always established. Treatment was finally withdrawn because of tolerability problems in only three of the 149 cases (2%). Bearing in mind the very varied nature of the severe, life-threatening infections reported here, two comments may be made: Intravenous rifampicin is useful and even life-saving in both severe tuberculous and non-tuberculous infections. It is safe even in long-term administration. However, treatments lasting over 30-60 days appear to involve a higher risk of venous thrombophlebitis.

1. **[Hepatotoxicity of rifampicin and isoniazid in the treatment of tuberculous meningitis (author's transl)].**
Frontera Izquierdo P. Anales espanoles de pediatria 1981;15(6):549-552.

Thirty four children with tuberculous meningitis were treated with rifampicin (mean, 17 mg/kg/day) and isoniazid (mean, 18 mg/kg/day). Fifteen (44%) showed rise in transaminase GOT and GPT values and four cases (11.7%) developed jaundice, hepatomegaly and low prothrombin levels. Rifampicin was removed in only nine of these 15 cases with signs of liver disfunction, but complete normalization of liver function and disappearance of symptoms occurred in all cases even when the treatment was not interrupted. Children are more sensitive to hepatic injury during rifampicin and isoniazid combination therapy than adults. Our results indicate very good prognosis for this hepatopathy and suggest that rifampicin need not be withdrawn in the benign situations. Removal of the rifampicin treatment may delay recovery of serious cases of tuberculous meningitis.

1. **[Hydrazide-rifampicin: hepatotoxicity in children].**
Uriz Urzainqui S. Anales espanoles de pediatria 1981;15(4):401-403.

1. **Serum and cerebrospinal fluid proteins in tuberculous meningitis.**
Guindi S. European neurology 1980;19(4):247-251.

Serum and CSF protein electrophoresis was performed on cellulose acetate in 8 controls and 30 cases of tuberculous meningitis before treatment and during a hospitalization period of 5 months. The analysis of the CSF electrophoretic pattern showed that abnormalities in the prealbumin, beta and gamma fractions may still exist as late as 5 months after initiation of treatment. An increase in alpha 2 and decrease in the albumin fractions in the serum also persisted. Treatment for 20 weeks improved the clinical condition of the patients and resulted in a significant improvement in the CSF prealbumin and alpha 1 fractions. These findings indicate that changes in these fractions may be considered a good prognostic aid.

1. **[Multiple cerebral tuberculomata involving brainstem and cerebellum--report of a case (author's transl)].**
Sato M. No to shinkei = Brain and nerve 1980;32(4):403-406.

A case of multiple cerebral tuberculomata involving the pons and cerebellum was presented. The lesions were demonstrated by CT as isodense to slightly dense foci. All four intra-axial lesions showed homogeneous enhancement following an intravenous injection of the contrast medium, and one of them was surrounded by a small area of low density, probably representing the perifocal edema. The patient responded well to chemotherapy with streptomycin, hydrazid and rifampicin : cranial nerve signs and long tract signs clearing rapidly and the enhancing lesions and mass effect on CT disappearing concomitantly. Although cerebral tuberculoma is nowadays very rare in Japan, still a high index of suspicion should always be entertained during the investigation of patients showing solitary or multiple enhancing lesions with no or slight degree of perifocal edema on CT, and a trial of antituberculous drugs should be given before the incurable malignancy is presumed or the lesion is explored surgically.

1. **Diagnosis and management of tuberculous paraplegia with special reference to tuberculous radiculomyelitis.**
Freilich D. Journal of neurology, neurosurgery, and psychiatry 1979;42(1):12-18.

Paraplegia occurred in eight of 17 patients with central nervous system tuberculosis. In six of these paraplegia was the presenting feature. Paraplegia may complicate tuberculous meningitis, or vertebral tuberculosis, but it may also occur, as in three of our cases, as a primary localised spinal tuberculous radiculomyelitis. These cases are presented in relation to the concept that paraplegia complicating these forms of tuberculosis is caused by radiculomyelitis.

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1. **Drug treatment of tuberculous meningitis in childhood. A survey of current practices**
McKenzie M.S. Clinical Pediatrics 1979;18(2):75-84.

Treatment of tuberculous meningitis with proper chemotherapy should be started immediately if a significant percentage of patients are to survive. Delay in diagnosis enhances the likelihood of late neurologic sequelae. The best recommended therapy for TBM in children seems to consist of utilizing at least 3 first-line drugs; isoniazid, rifampin, and streptomycin. While many protocols add ethambutol to their initial drug regimens, monitoring for side effects in young children is difficult with this agent. Isoniazid and rifampin are the two most potent antituberculous drugs to date. Both drugs penetrate into the cerebrospinal fluid in acceptable concentrations and are well tolerated by children. Hepatoxicity is the most significant side effect from isoniazid and rifampin administration, and liver function tests should be performed periodically. Streptomycin has been used to treat TBM since 1947 and probably should be included in drug therapy protocols. The drug penetrates poorly into the cerebrospinal fluid and only in the presence of inflamed meninges. Ototoxicity is its main adverse effect. Ethambutol has replaced para-aminosalicylic acid in some drug therapy protocols because of the ease of administration of the drug (once a day dosage), but toxicity is difficult to recognize in children.

1. **Effectiveness of intravenous tuberculostatic therapy of patients with tuberculous meningoencephalitis**
Ivaniuta O.M. Vrachebnoe Delo 1979;:98-100.

1. **The treatment of tuberculous meningitis in children with A combination of isoniazid, rifampicin and streptomycin (a preliminary report).**
Rahajoe N. N Paediatrica Indonesiana 1979;19(11-12):285-294.

1. **Tuberculous meningitis.**
Kovanen J. Acta neurologica Scandinavica 1979;59(2-3):127-134.

Ten patients with confirmed tuberculous meningitis were seen at Meilahti Hospital, University of Helsinki, in 1966--1977. Six of the patients had a positive CSF culture for M. tuberculosis, and a positive CSF smear for acid-fast bacilli was found in one case. On admission, seven patients had an altered state of consciousness, five complained of headache, and nuchal rigidity was noted in two. Five patients recovered completely, three had persistent late sequelae, and two of the patients died. The most important fact influencing the prognosis was an early institution of adequate antituberculous chemotherapy.

1. **[Acute tuberculous meningitis in children. A report on 4 cases (author's transl)].**
Ollivier A. La semaine des hopitaux : organe fonde par l'Association d'enseignement medical des hopitaux de Paris 1979;55(35-36):1636-1640.

Four children were treated for acute tuberculous meningitis. One child died and 2 others were left with severe neurological sequellae. The diagnostic and clinical signs of tuberculous meningitis are reviewed. Treatment includes the administration of an association of INH-rifampicine and ethambutol orally, or INH-ethambutol-ethionamide intravenously when oral administration is impossible. Intrathecal injections of rifamycine SV can be given for acute forms. Corticoids have only one indication: intracranial hypertension with cerebral edema, which requires surgical decompression if no improvement is obtained. The fact that cases of tuberculous meningitis are still notified, is a justification for early BCG vaccination and regular control of the tuberculin allergic reaction.

1. **[Principles underlying the use of antituberculosis medication in children (author's transl)].**
Ollivier A. La semaine des hopitaux : organe fonde par l'Association d'enseignement medical des hopitaux de Paris 1979;55(33-34):1529-1535.

The authors review the principles underlying antituberculosis therapy in children. Basing their comment on the published literature, they analyze the properties, pharmacology, toxicity, and side-effects of each medication, and define their dosage and modes of administration.

1. **Common bacterial infections in infancy and childhood. II. Infections of the central nervous system**
Ahronheim G.A. Current Therapeutics 1978;19(7):145-161.

1. **DISTURBIOS METABLICOS IMPORTANTES ASOCIADOS A LA ADMINISTRACION DE ACIDO PARA-AMINOSALICILICOSevere metabolic disturbances after administration of para-aminosalicylic acid**
Miquel Servert J. Revista Clinica Espanola 1978;148(6):639-641.

1. **LA MENINGITE TUBERCULEUSE DE L'ENFANT: A PROPOS DE 3 OBSERVATIONS RECENTESTuberculous meningitis in children (3 recent cases)**
Despert F. Revue de Medecine de Tours 1978;12(1):18-24.

1. **Rifampicin in the treatment of tuberculous meningitis.**
Girgis N. I The Journal of tropical medicine and hygiene 1978;81(12):246-247.

Seventy-one patients diagnosed to have tuberculous meningitis were treated with isoniazid, streptomycin plus either rifampicin (36 patients or ethambutol (35 patients). Results of therapy were identical in both treatment-groups (approximately 50 per cent mortality). Rifampicin appears to be as effective as ethambutol in the treatment of this infection.

1. **Rifampin in treatment of tuberculous meningitis in children.**
Sunakorn P. Journal of the Medical Association of Thailand = Chotmaihet thangphaet 1978;61(2):93-98.

1. **Spontaneous recovery in meningitis with TB bacilli in the cerebrospinal fluid.**
Hurmuzache T. Revista medico-chirurgicala a Societatii de Medici si Naturalisti din Iasi 1978;82(3):405-410.

1. **The treatment of tuberculous meningitis.**
Fallon R. J The Journal of antimicrobial chemotherapy 1978;4(1):1-2.

1. **[Combined forms of tuberculous meningitis and osteoarticular tuberculosis].**
Tarasova E. F Problemy tuberkuleza 1978;(4):52-56.

1. **Advances in the treatment of tuberculosis.**
Clarke P. D Journal of the Royal Naval Medical Service 1976;62(2):85-91.

1. **Editorial: Treatment of tuberculous meningitis.**
Anon. Lancet (London, England) 1976;1(7963):787-788.

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1. **Some aspects of tuberculous meningitis in Surabaya.**
Chandra B. Proceedings of the Australian Association of Neurologists 1976;13:73-81.

Eighty tuberculous meningitis patients who were seen in the neurological clinics in Surabaya between the January 1971 and January 1975 were asked to cooperate in a double blind clinical trial. One group was given isoniazid, streptomycin and p-aminosalicylic acid, the other group was given isioniazid, rifampicin, ethambutol and a protease. The outcome after the treatment with isoniazid, rifampicin and ethambutol was significantly better than that with isoniazed, streptomycin and p-aminosalicylic acid. The clinical and laboratory symptoms and signs are reviewed in detail.

1. **Tuberculous meningitis in childhood. Forty-three cases.**
Idriss Z. H American journal of diseases of children (1960) 1976;130(4):364-367.

Forty-three patients in the pediatric age group had tuberculous meningitis. Therapy included the use of adrenocorticosteroids. All four patients who were in stage 1 on admission to the hospital, seven of the 33 in stage 2, and one of the six in stage 3 (coma) recovered without gross neurological sequelas. Eight patients died, and the remaining 23 recovered, with late neurological sequelas. Early diagnosis and appropriate treatment determine the prognosis of tuberculous meningitis.

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1. **Editorial: Rifampin in tuberculous meningitis.**
Sifontes J. E The Journal of pediatrics 1975;87(6):1015-1017.

1. **Evaluation of rifampicin in the treatment of tuberculous meningitis in children.**
Visudhiphan P. The Journal of pediatrics 1975;87(6):983-986.

Of the 20 patients given rifampicin and isoniazid, 19 survived and one died. Twelve patients recovered from the disease without any significant neurologic defect. Seven patients had moderate to severe handicaps which included hemiparesis in four, hydrocephalus in two,mental retardation in three, and blindness in one. There was no hearing deficit. The average hospital stay in this group was 3-1/2 weeks. Among the 13 patients given streptomycin, PAS, and isoniazid, four are dead. Only three patients recovered with a completely good condition. The remainder had either single or multiple neurologic defects. The moderate degree of nerve deafness was also observed in two patients.

1. **Experimental and clinical data on intravenous treatment of tuberculous meningitis (Russian)**
Nazarenko V.G. Vrachebnoe Delo 1975;:92-95.

Experimental investigations of the bacteriostatic activity of the blood, cerebrospinal fluid and cerebral tissue were carried out in healthy and tuberculous meningitis rabbits in condition of routine and IV administration of streptomycin, tubazide and PAS. It was found that these indices were significantly higher during the IV method of administration of antibacterial agents. Clinical investigations indicate that in treatment of tuberculous meningitis in the adult complex therapy including steroid hormones and IV administrations of the 3 main antitubercular agents proved most efficient.

1. **Tuberculous meningitis in childhood.**
Smith A. L The Medical journal of Australia 1975;1(3):57-60.

The 43 cases of tuberculous meningitis treated at the Royal Children's Hospital, Melbourne, over the 15-year period from January, 1954, to December, 1969, are reviewed in detail. With "triple drug" antituberculosis therapy, 19 patients made a full recovery and seven died. Of the other 17, 11 had major permanent sequelae. There was a strong correlation between the patient's state of consciousness at the time antituberculosis therapy was commenced and the ultimate result. Suggestions are made on how the mortality and morbidity can be reduced.

1. **[Experimental and clinical data on the intravenous therapy of tuberculosis meningitis].**
Nazarenko V. G Vrachebnoe delo 1975;(3):92-95.

1. **LA MENINGITE TUBERCOLARE NELL'ADULTOTubercular meningitis in adults**
Bolletti M. Giornale di Malattie Infettive e Parassitarie 1974;26(5):525-533.

In the last 2 decades the frequency of meningitis is more and more shifting from infancy to post pubescent and adult age. The authors describe 18 cases which they observed in adult people in the period 1967-1972. On the basis of a marked increase of deaths observed in the more recent years, they conclude that the phenomenon is to be ascribed mainly to 2 causes: an often unjustified delay in the diagnosis with a consequent delay in the starting of the specific therapeutic treatment; an increase in the chemoantibiotic resistant strains. Finally the need of an antibiotic gram, to be carried out on the isolated strain, is stressed in order to administer massive doses of the chemoantibiotic drug which appears to be the most active.

1. **Letter: In-vitro detection of hypersensitivity to antituberculous drugs.**
Baker J. T Lancet (London, England) 1974;2(7886):967-969.

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1. **MENINGITE TUBERCULEUSE DE L'ENFANT. (ETUDE DE 70 CAS)Tuberculous meningitis in children (70 cases)**
Jedidi H. Tunisie Medicale 1974;52(1):19-27.

After a study of the clinical signs, the treatment and the late sequelae, the authors draw the following conclusions from their investigation of 70 children suffering from tuberculous meningitis. Although it occurs less frequently, tuberculous meningitis of children involves especially the young child and often assumes a very serious aspect. The diagnosis cannot be made in an early stage, and consequently the institution of treatment is also late. The prognosis therefore remains very bad. The early mortality is high. The children who survive suffer from severe sequelae. Continuation of treatment outside hospital after normalization of the cerebrospinal fluid and with a satisfactory clinical condition, does not constitute a prudent attitude. Relapses have been observed and there is no certainty of a regularly continued treatment at home. The authors therefore recommend a regular surveillance by keeping the patients in hospital for 18 to 24 mth. They are of the opinion that only early BCG vaccination (at birth) and a regular check on tuberculin allergy will protect these children against this redoubtable disease.

1. **Mixed pneumococcal and tuberculous meningitis**
Levinsky R.J. Archives of Disease in Childhood 1974;49(4):325-328.

A case of mixed meningitis in a young infant involving S. pneumoniae and M. tuberculosis is reported that emphasizes the diagnostic difficulties and the importance of searching for tubercle bacilli at the slightest suspicion.

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1. **Mycobacterium tuberculosis infection of the middle ear.**
Sahn S. A Chest 1974;66(1):104-106.

1. **Unusual presentations of tuberculous meningitis**
Meyers B.R. Mount Sinai Journal of Medicine 1974;41(3):407-411.

Three cases of tuberculous meningitis with unusual presentation occurring in previously healthy females are presented. It is suggested that this diagnosis be considered in every patient with explained neurologic manifestations and meningitis, whether polymorphonuclear cells predominate in the cerebrospinal fluid or the glucose and protein content are normal. Therapy with at least isoniazid should be started while the diagnostic investigation is pursued.

1. **[Chronic tuberculous meningitis in a case of known Mycobacterium kansasii infection].**
Tauchnitz C. Zeitschrift fur die gesamte innere Medizin und ihre Grenzgebiete 1974;29(12):494-497.

1. **Acute forms of tuberculosis.**
Felton C. P The Medical clinics of North America 1973;57(6):1394-1402.

1. **Vnutrivennaia khimioterapiia bol'nykh tuberkulezom legkikhIntravenous chemotherapy of pulmonary tuberculosis**
Ivaniuta O.M. Vrachebnoe delo 1971;(1):84-87.

1. **Vnutrivennaia khimioterapiia tuberkuleza legkikh i tuberkuleznogo meningita u detei i podrostkovIntravenous chemotherapy of pulmonary tuberculosis and tuberculous meningitis in children and adolescents**
Kibrik B.L. Sovetskoe zdravookhranenie Kirgizii 1971;1:56-59.

1. **[Intravenous chemotherapy of pulmonary tuberculosis and tuberculous meningitis in children and adolescents].**
Kibrik B. L Sovetskoe zdravookhranenie Kirgizii 1971;1:56-59.

1. **[Intravenous chemotherapy of pulmonary tuberculosis].**
Ivaniuta O. M Vrachebnoe delo 1971;(1):84-87.

1. **[Therapy of meningitides].**
Bender F. Bibliotheca psychiatrica et neurologica 1969;139:635-647.

1. **[ETHIONAMIDE IN THE TREATMENT OF TUBERCULOUS MENINGITIS. IMPORTANCE OF INTRAVENOUS ADMINISTRATION].**
FOUQUET J. Giornale italiano di chemioterapia 1963;10:105-109.

1. **[Association of isoniazid and ethionamide in the treatment of tuberculous meningitis. (Superiority of intravenous administration)].**
FOUQUET J. Revue de tuberculose et de pneumologie 1962;26:469-487.

1. **[Association of isoniazid and ethionamide in the treatment of tuberculous meningitis. Superiority of intravenous administration].**
FOUQUET J. Bulletins et memoires de la Societe medicale des hopitaux de Paris 1962;113:411-425.

1. **[Isoniazid-ethioniamide combination in the treatment of tuberculous meningitis. Superiority of administration by venous route].**
FOUQUET J. La Semaine des hopitaux: therapeutique 1962;38:905-908.

1. **[Streptomycin-PAS-isoniazid combination in treatment of tuberculous meningitis].**
CONESE G. Il Policlinico. Sezione pratica 1954;61(11):337-346.

1. **[Advantages of streptomycin and nicotinic acid isomers combination in treatment of tuberculous meningitis in infants].**
PIERRET R. L'echo medical du nord 1953;24(1-2):9-15.

1. **[Treatment of tuberculous meningitis with intramuscular and intraspinal streptomycin and with intravenous PAS, addition of isonicotinic acid hydrazide].**
BAGUENA CANDELA R. Medicina espanola 1953;29(170):412-435.

1. **[Effect of intravenously administered insulin on the cerebrospinal fluid sugar level in children treated by streptomycin].**
FOJUDZKI E. Pediatria polska 1952;27(1):35-41.

1. **[Late results of combined chemotherapy of tuberculous meningitis in 37 cases; PAS and streptomycin].**
MOESCHLIN S. Helvetica medica acta 1951;18(4-5):441-448.

1. **Treatment of miliary and meningeal tuberculosis in infants and children.**
PERRY T. L California medicine 1950;72(3):159-163.

Streptomycin and combined streptomycin-promizole treatment of miliary and meningeal tuberculosis in infants and children at the Los Angeles Children's Hospital has resulted in clear-cut arrests in seven patients, two of whom had meningitis. A much longer period of observation will be necessary before these patients may be considered cured. These results are incomparably better than the universally fatal outcome of both diseases in a large and unselected group of untreated cases which has been studied. Promizole, and possibly also para-aminosalicylic acid, should be given concurrently with streptomycin. As they are relatively harmless drugs, they should be given to ambulatory patients for a long period of time after arrest of the disease to decrease the likelihood of recurrence. If necessary, streptomycin may be given for longer than 90 days, or in second courses, since combined chemotherapy apparently delays the appearance of streptomycin-resistant strains of tubercle bacilli. The current pessimism with which many pediatricians view miliary and meningeal tuberculosis is unwarranted. Optimism will be rewarded with many more recoveries in the future.

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## B. Search History

|  | **Source** | **Criteria** | **Results** |
| --- | --- | --- | --- |
| 1. | Medline | "TUBERCULOSIS, MENINGEAL"/ | 6850 |
| 2. | Medline | ((TB OR tubercul\*) ADJ2 mening\*).ti,ab | 6694 |
| 3. | Medline | ((TB OR tubercul\*) ADJ2 (brain OR cerebral OR neurological)).ti,ab | 929 |
| 4. | Medline | (1 OR 2 OR 3) | 9166 |
| 5. | Medline | exp ANTI-BACTERIAL AGENTS / | 658150 |
| 6. | Medline | ((anti-bacterial OR anti-mycobacterial OR antibacterial OR antimycobacterial OR bacteriocidal) ADJ1 (agent\* OR compound\*)).ti,ab | 9703 |
| 7. | Medline | (antibiotic\* OR anti-biotic\* OR anti-microbial OR antimicrobial\*).ti,ab | 391914 |
| 8. | Medline | (5 OR 6 OR 7) | 849977 |
| 9. | Medline | (4 AND 8) | 2673 |
| 10. | Medline | (intensif\*).ti,ab | 27057 |
| 11. | Medline | (9 AND 10) | 11 |
| 12. | EMBASE | "TUBERCULOUS MENINGITIS"/ | 6409 |
| 13. | EMBASE | ((TB OR tubercul\*) ADJ2 mening\*).ti,ab | 5995 |
| 14. | EMBASE | ((TB OR tubercul\*) ADJ2 (brain OR cerebral OR neurological)).ti,ab | 831 |
| 15. | EMBASE | (12 OR 13 OR 14) | 8843 |
| 16. | EMBASE | exp "ANTIBIOTIC AGENT"/ | 1222782 |
| 17. | EMBASE | ((anti-bacterial OR anti-mycobacterial OR antibacterial OR antimycobacterial OR bacteriocidal) ADJ1 (agent\* OR compound\*)).ti,ab | 11832 |
| 18. | EMBASE | (antibiotic\* OR anti-biotic\* OR anti-microbial OR antimicrobial\*).ti,ab | 516096 |
| 19. | EMBASE | (16 OR 17 OR 18) | 1422112 |
| 20. | EMBASE | (15 AND 19) | 1892 |
| 21. | EMBASE | (intensif\*).ti,ab | 48787 |
| 22. | EMBASE | (20 AND 21) | 11 |
| 23. | Medline | ((increas\* OR higher OR greater OR larger OR non-standard OR nonstandard) ADJ2 (dose OR course OR treatment OR therapy OR regimen)).ti,ab | 198218 |
| 24. | Medline | "DRUG THERAPY, COMBINATION"/ | 156462 |
| 25. | Medline | ((combination OR additional) ADJ2 (dose OR course OR treatment OR therapy OR regimen)).ti,ab | 98861 |
| 26. | Medline | ISONIAZID/ | 17997 |
| 27. | Medline | (isoniazid).ti,ab | 14320 |
| 28. | Medline | ETHAMBUTOL/ | 3764 |
| 29. | Medline | (ethambutol).ti,ab | 4769 |
| 30. | Medline | PYRAZINAMIDE/ | 3075 |
| 31. | Medline | (pyrazinamide).ti,ab | 3471 |
| 32. | Medline | LINEZOLID/ | 2608 |
| 33. | Medline | (linezolid).ti,ab | 4950 |
| 34. | Medline | (moxifloxacin).ti,ab | 4006 |
| 35. | Medline | LEVOFLOXACIN/ | 2920 |
| 36. | Medline | (levofloxacin).ti,ab | 6618 |
| 37. | Medline | STREPTOMYCIN/ | 21618 |
| 38. | Medline | (streptomycin).ti,ab | 19951 |
| 39. | Medline | ETHIONAMIDE/ | 1273 |
| 40. | Medline | (ethionamide).ti,ab | 895 |
| 41. | Medline | exp "ADMINISTRATION, INTRAVENOUS"/ | 136688 |
| 42. | Medline | (intravenous ADJ (adminstration OR infusion OR dose OR course OR treatment OR therapy OR regimen)).ti,ab | 33103 |
| 43. | Medline | (23 OR 24 OR 25) | 423600 |
| 44. | Medline | (41 OR 42) | 158915 |
| 45. | Medline | (26 OR 27 OR 28 OR 29 OR 30 OR 31 OR 32 OR 33 OR 34 OR 35 OR 36 OR 37 OR 38 OR 39 OR 40) | 66653 |
| 46. | Medline | exp "ANTIBIOTICS, ANTITUBERCULAR"/ | 41976 |
| 47. | Medline | ((antitubercular OR tuberculostatic) ADJ (treatment OR therapy OR regimen)).ti,ab | 1152 |
| 48. | Medline | (46 OR 47) | 43043 |
| 49. | Medline | (45 OR 48) | 102036 |
| 50. | Medline | (43 OR 44) AND 49 | 10355 |
| 51. | Medline | (9 AND 50) | 158 |
| 52. | EMBASE | ((increas\* OR higher OR greater OR larger OR non-standard OR nonstandard) ADJ2 (dose OR course OR treatment OR therapy OR regimen)).ti,ab | 183035 |
| 53. | EMBASE | \*"DRUG COMBINATION"/ | 2250 |
| 54. | EMBASE | ((combination OR additional) ADJ2 (dose OR course OR treatment OR therapy OR regimen)).ti,ab | 121867 |
| 55. | EMBASE | ISONIAZID/ | 54009 |
| 56. | EMBASE | (isoniazid).ti,ab | 17629 |
| 57. | EMBASE | ETHAMBUTOL/ | 27872 |
| 58. | EMBASE | (ethambutol).ti,ab | 6840 |
| 59. | EMBASE | PYRAZINAMIDE/ | 22124 |
| 60. | EMBASE | (pyrazinamide).ti,ab | 4700 |
| 61. | EMBASE | LINEZOLID/ | 17476 |
| 62. | EMBASE | (linezolid).ti,ab | 7197 |
| 63. | EMBASE | (moxifloxacin).ti,ab | 5733 |
| 64. | EMBASE | LEVOFLOXACIN/ | 31026 |
| 65. | EMBASE | (levofloxacin).ti,ab | 10460 |
| 66. | EMBASE | STREPTOMYCIN/ | 51063 |
| 67. | EMBASE | (streptomycin).ti,ab | 18204 |
| 68. | EMBASE | ETHIONAMIDE/ | 5294 |
| 69. | EMBASE | (ethionamide).ti,ab | 1009 |
| 70. | EMBASE | "INTRAVENOUS DRUG ADMINISTRATION"/ | 370088 |
| 71. | EMBASE | (intravenous ADJ (adminstration OR infusion OR dose OR course OR treatment OR therapy OR regimen)).ti,ab | 35033 |
| 72. | EMBASE | (52 OR 53 OR 54) | 301692 |
| 73. | EMBASE | (70 OR 71) | 389820 |
| 74. | EMBASE | (55 OR 56 OR 57 OR 58 OR 59 OR 60 OR 61 OR 62 OR 63 OR 64 OR 65 OR 66 OR 67 OR 68 OR 69) | 150357 |
| 75. | EMBASE | exp "TUBERCULOSTATIC AGENT"/ | 150733 |
| 76. | EMBASE | ((antitubercular OR tuberculostatic) ADJ (treatment OR therapy OR regimen)).ti,ab | 1504 |
| 77. | EMBASE | (75 OR 76) | 151192 |
| 78. | EMBASE | (74 OR 77) | 225605 |
| 79. | EMBASE | (72 OR 73) AND 77 | 7168 |
| 80. | EMBASE | 20 AND 79 | 89 |

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