J Microbiol Immunol Infect
2004;37:382-384

Guidelines for chemotherapy of tuberculosis in Taiwan

Infectious Diseases Society of the Republic of China; The Society of Tuberculosis, Taiwan; Medical Foundation in Memory of Dr. Deh-Lin Cheng; Foundation of Professor Wei-Chuan Hsieh for Infectious Diseases Research and Education; and CY Lee's Research Foundation for Pediatric Infectious Diseases and Vaccines

Tuberculosis is a major health problem in Taiwan and worldwide. Despite concerted efforts of health authorities to control tuberculosis, the incidence and prevalence of tuberculosis in Taiwan remains high (64.84/100,000 and 5.56/100,000 in 2001). Most cases of tuberculosis are now seen and treated by primary care physicians in the community.

A consensus meeting was convened on March 10, 2004 to establish guidelines for the chemotherapy of tuberculosis. This was preceded by a collaborative symposium on tuberculosis held by the Infectious Diseases Society of the Republic of China (IDSROC), the Medical Foundation in Memory of Dr. Deh-Lin Cheng, Foundation of Professor Wei-Chuan Hsieh for Infectious Diseases Research and Education, and CY Lee's Research Foundation for Pediatric Infectious Diseases and Vaccines. Participants of the consensus meeting included board members of the IDSROC, and experts in infectious diseases, chest medicine, and tuberculosis.* Three principles were maintained in establishing these guidelines:

1. Establishment of guidelines from the viewpoint of primary care physicians.
2. Antimicrobial agents recommended in the guidelines are agents already marketed in Taiwan.
3. Guidelines were based on academic principles rather than the regulations of the Bureau of National Health Insurance on antibiotic usage.

Many recommendations were based on expert opinion and unpublished data, due to the lack of randomized, controlled, clinical trials in the area. Topics not included in the scope of these guidelines are: treatment of TB-human immunodeficiency virus (HIV) coinfection, drug-drug interactions, several anti-tuberculous drugs (rifabutin, cycloserine) and treatment of the pediatric population.

This guideline was approved by the board of IDSROC, and a copy will be sent to primary care physicians, the setting where most cases of tuberculosis are treated. The document is published in the *Journal of Microbiology, Immunology and Infection*, to serve as an easily accessible reference to all practising physicians in Taiwan.

Guidelines for chemotherapy of tuberculosis

Pulmonary tuberculosis	Drugs of choice	Alternative
I. New case		
1. Standard regimen	INH + RIF + EMB + PZA for 2 months, then INH + RIF + EMB for 4 months[a]	—
2. Fixed-dose combinations	Rifater[b] + EMB for 2 months then Rifinah[c] + EMB for 4 months[a]	—
II. Retreatment[d]		
1. Relapse[e]	INH + RIF + EMB + PZA + IA[f] for 3 months, then INH + RIF + EMB for 5 months	—
2. Default[g]	INH + RIF + EMB + PZA + IA[f] for 3 months, then INH + RIF + EMB for 5 months	—
3. Failure[h]	INH + RIF + EMB + PZA + IA[f] for 3 months, then INH + RIF + EMB for 5 months	—
III. Drug resistance		
1. INH	RIF + EMB + PZA for 6 months	RIF + EMB + PZA + IA[f] for 6 months
2. RIF	INH + EMB + PZA for 9-12 months	INH + EMB + PZA + IA[f] ± FQ[i] for 9 months
3. EMB	INH + RIF + PZA for 2 months, then INH + RIF for 4 months	—

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4. INH, RIF (MDR-TB)	EMB + PZA + TBN + IA[f] + FQ[i] for 18-24 months[j]	—
5. INH, RIF, EMB (MDR-TB)	PZA + TBN + PAS + IA[f] + FQ[i] for 18-24 months[j]	—
IV. Intolerance		
1. INH	RIF + EMB + PZA for 6 months	—
2. RIF	INH + EMB + PZA for 9-12 months	INH + EMB + PZA + IA[f] for 9 months
3. EMB	INH + RIF + PZA for 2 months, then INH + RIF for 4 months	—
4. PZA	INH + RIF + EMB for 9 months	—
5. INH, RIF	EMB + PZA + TBN + IA[f] + FQ[i] for 18-24 months[j]	—
V. Special situations		
1. Liver function impairment and/or liver cirrhosis	RIF + EMB + PZA for 6 months or INH + RIF + EMB for 9 months	RIF + EMB + IA[f] + FQ[i] for 12-18 months or EMB + TBN + IA[f] + FQ[i] for 18-24 months
2. Renal function impairment[k] or ESRD	INH + RIF + EMB[l] + PZA[l] for 2 months, then INH + RIF + EMB[l] for 4 months	INH + RIF + EMB + PZA for 2 months, then INH + RIF + EMB for 4 months[m]
3. Pregnancy or breastfeeding	INH + RIF + EMB + PZA for 2 months, then INH + RIF + EMB for 4 months	INH + RIF + EMB for 9 months

Extra-pulmonary tuberculosis	**Drugs of choice**	**Alternative**
I. Pleurisy Lymphadenitis Peritonitis (intestinal disease) Pericarditis[n] Genito-urinary tract diseases	INH + RIF + EMB + PZA for 2 months, then INH + RIF + EMB for 4 months	—
II. Bone and joint diseases Pleural empyema	INH + RIF + EMB + PZA for 2 months, then INH + RIF + EMB for 7 months	—
III. Meningitis[n] CNS disease[n]	INH + RIF + EMB + PZA for 2 months, then INH + RIF + EMB for 10 months	—

Dosage of anti-tuberculous agents (for adults only)	
Rifater (INH 80 mg + RIF 120 mg + PZA 250 mg)	1 tab/10 kg BW qd (maximum 5 tab)
Rifinah-300 (INH 150 mg + RIF 300 mg)	2 tab qd, if BW >50 kg BW
Rifinah-150 (INH 100 mg + RIF 150 mg)	3 tab qd, if BW <50 kg BW
INH	5 mg/kg BW qd (maximum 300 mg)
RIF	10 mg/kg BW qd (maximum 600 mg)
EMB	15-25 mg/kg BW qd
PZA	15-30 mg/kg BW qd (maximum 2g)
Streptomycin, amikacin, kanamycin	15 mg/kg BW qd
TBN	15-20 mg/kg BW, divided to bid-tid (maximum 1 g)
PAS	200 mg/kg BW, divided to bid-qid
Ofloxacin	400 mg bid
Ciprofloxacin	500-750 mg bid
Levofloxacin	500 mg qd

Abbreviations: INH = isoniazid; RIF = rifampin; EMB = ethambutol; PZA = pyrazinamide; IA = injectable aminoglycosides; FQ = fluoroquinolones; MDR-TB = multi-drug resistant *Mycobacterium tuberculosis*; TBN = prothionamide; PAS = para-aminosalicylic acid; ESRD = end-stage renal disease; CNS = central nervous system; BW = body weight; qd = once daily; bid = twice a day; tiw = 3 times weekly; tid = 3 times a day; qid = 4 times a day; qod = once every other day; tab = tablet(s); Ccr = creatinine clearance

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[a]Cavitation on initial chest X-ray and/or positive cultures at completion of initial 2 months' treatment, extend treatment to 9 months.
[b]Dose of Rifater is 1 tab/10 kg BW qd, maximum 5 tab.
[c]Dose of Rifinah-300 is 2 tab qd for patients with BW >50 kg, and Rifinah-150 3 tab qd if BW <50 kg.
[d]Culture and susceptibility testing should be done immediately and regimen should be tailored to susceptibility testing results. Referral to specialists in infectious diseases, chest medicine or experts on tuberculosis is recommended.
[e]Relapse is defined as a patient who develops active tuberculosis (by culture, clinical or radiological deterioration) after completion of anti-tuberculous therapy.
[f]Injectable aminoglycosides include streptomycin, kanamycin, and amikacin, and should be administered in the initial 2 months of treatment.
[g]Default is defined as interruptions in therapy of longer than 2 months.
[h]Failure is defined as continued or recurrent positive cultures after 4 months of treatment in patients with assured adherence to the prescribed anti-tuberculous regimen.
[i]Fluoroquinolones include ofloxacin, ciprofloxacin and levofloxacin.
[j]Treatment duration is a total of 18 months after sputum conversion.
[k]Renal function impairment is defined as Ccr ≤30 mL/min.
[l]Doses should be reduced to EMB 15-25 mg/kg BW qod and PZA 12-25 mg/kg BW qd.
[m]Intermittent (3 times weekly) dosing after hemodialysis is INH 900 mg, RIF 600 mg, EMB 15-25 mg/kg BW and PZA 25-35 mg/kg BW.
[n]Steroids are recommended (prednisolone <1 mg/kg BW qd or equivalent) for a minimum of 3 weeks.

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