

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Mitnick CD, Shin SS, Seung KJ, et al. Comprehensive treatment of extensively drug-resistant tuberculosis. *N Engl J Med* 2008;359:563-74.

Table 1. Drug susceptibility testing methods and concentrations

Drug	Method	Medium	Concentration Tested (µg per milliliter)
First-line agents			
<i>Isoniazid</i>	proportion	7H10 agar	0.2, 1, 5
<i>Rifampin</i>	proportion	7H10 agar	1
<i>Ethambutol</i>	proportion	7H10 agar	5
<i>Pyrazinamide</i>	BACTEC	liquid	100
Aminoglycosides/polypeptides (injected)			
First-line			
<i>Streptomycin</i>	proportion	7H10 agar	2, 10
Second-line			
<i>Amikacin</i>	proportion	7H10 agar	4
<i>Kanamycin</i>	proportion	7H10 agar	5
<i>Capreomycin</i>	proportion	7H10 agar	10
Fluoroquinolones			
Early generation			
<i>Ciprofloxacin</i>	proportion	7H10 agar	1 ¹
<i>Ofloxacin</i>	proportion	7H10 agar	1
Late generation²			
<i>Levofloxacin</i> *	proportion	7H10 agar	1
<i>Gatifloxacin</i> *	proportion	7H10 agar	2
<i>Moxifloxacin</i> *	proportion	7H10 agar	2
Other second-line			
<i>Cycloserine</i>	proportion	7H10 agar	30
<i>Ethionamide</i>	proportion	7H10 agar	5
<i>Para-aminosalicylic acid</i>	proportion	7H10 agar	8

¹ The critical concentration for ciprofloxacin was reduced in 2001, from 2 to 1 µg per milliliter.

² Although added to the routine panel in 2001, no evidence-based critical concentrations existed for the newer fluoroquinolones. They were established by the laboratory at levels specified to provide some limited clinical guidance.

Table 2. Weight-based dosing of antituberculosis medications for adults¹

Medication (Presentation)	< 33 kg	33 – 50 kg	51 – 60 kg	> 60 kg
First-line agents				
<i>Ethambutol</i> (100, 400 mg)	25 mg/kg/day	800–1200 mg	1200–1600 mg	1600–2000 mg
<i>Pyrazinamide</i> (500 mg)	30–40 mg/kg/day	1000–1750 mg	1750–2000 mg	2000–2500 mg
Aminoglycosides/polypeptides (injected)				
First-line				
<i>Streptomycin</i> (1 gram vial)	15–20 mg/kg/day	500–750 mg	1000 mg	1000 mg
Second-line				
<i>Amikacin</i> (1 gram vial)	15–20 mg/kg/day	500–750 mg	1000 mg	1000 mg
<i>Kanamycin</i> (1 gram vial)	15–20 mg/kg/day	500–750 mg	1000 mg	1000 mg
<i>Capreomycin</i> (1 gram vial)	15–20 mg/kg/day	500–750 mg	1000 mg	1000 mg
Fluoroquinolones				
First generation				
<i>Ciprofloxacin</i> (250, 500, 750 mg)	20–30 mg/kg/day	1500 mg	1500 mg	1500 mg

¹ Partners In Health. The PIH Guide to the Medical Management of Multidrug-Resistant Tuberculosis. Boston, MA: Partners In Health; 2003.

<i>Ofloxacin</i> (200, 300, 400 mg)	Usual adult dose for MDR TB is 800 mg	800 mg	800 mg	800 mg
Later generation				
<i>Levofloxacin</i> (250, 500 mg)	Usual adult dose for MDR TB is 750 mg	750 mg	750 mg	750 mg
<i>Moxifloxacin</i> (400 mg)	Usual adult dose for MDR TB is 400 mg	400 mg	400 mg	400 mg
<i>Gatifloxacin</i> (400 mg)	Usual adult dose for MDR TB is 400 mg	400 mg	400 mg	400 mg
Other second-line				
<i>Cycloserine</i> (250 mg)	15 mg/kg/day	500 mg	750 mg	1000 mg
<i>Ethionamide</i> (250 mg)	15–20 mg/kg/day	500 mg	750 mg	1000 mg
<i>Prothionamide</i> (250 mg)	15–20 mg/kg/day	500 mg	750 mg	1000 mg
<i>PAS</i> (4 gram sachets, Jacobus PASER®)	150 mg/kg/day	8 grams	8 grams	8 grams
Agents with questionable activity against MDR-TB				
<i>Isoniazid</i> (100, 300 mg)	4–6 mg/kg/day or high-dose: 15 mg/kg 2x/wk	200–300 mg daily or high-dose: 600–900 mg 2x/wk	300 mg daily or high-dose: 900 mg 2x/wk	300 mg daily or high-dose: 900 mg 2x/wk
<i>Rifampin</i> (150, 300 mg)	10–20 mg/kg/day	450–600 mg	600 mg	600 mg

<i>Rifabutin</i> (150 mg)	5 mg/kg/day	200–300 mg	300 mg	300 mg
<i>Clarithromycin</i> (500 mg)	15 mg/kg/day	1000 mg	1000 mg	1000 mg
<i>Amoxicillin-clavulanate</i> (500/125 mg or 875/125 mg)	45 mg/kg/day (based on the amox- icillin component)	2 grams or 1.65 grams	2 grams or 1.65 grams	2 grams or 1.65 grams
<i>Clofazimine</i> (50,100 mg)	3-5 mg/kg/day	200-300 mg	200-300 mg	200-300 mg

Note: The above doses are given as the total daily doses. The following medications are usually given twice daily: ciprofloxacin, ofloxacin, ethionamide, prothionamide, cycloserine, PAS, and amoxicillin/clavulanate and clarithromycin. For example, ethionamide (750 mg) is usually given 500 mg for the morning and 250 mg for the evening.

Table 3. Regimen Details

ID	Months Tx	First line Orals			Injectables			Fluoroquinolones				Other Second Line			Other			Outcome	
		EMB	PZA	AMK	CM	KM	SM	CPX	OFX	LFX	MFX	CS	ETH	PAS	AUG	CRT	CFZ		RFB
1 ^a	31m	954		863					864	90	954		954	954		954			Cured
2	26m		792				792		792		792		792	792		792			Cured
3	24m	734					395		469	265	734	734	734	734	486	460			Cured
4 ^{NS}	26m		777				475		409		777		777	777	465				Cured
5 ^a	25m		763				763		763		763	763				763			Cured
6	28m						676		108	739	847	847	847	847		847	847	847	Cured
7	26m		796			562			562	234	796		796	796	234	796			Cured
8	24m		737			240				737	737	737	737	737		737			Cured
9	30m		924							921	921	924	921	921	789		789		Cured
10	27m		34	550	34					34	819	833	833	833	626		833		Cured
11	30m				686					900	900	900	900	900		900			Cured
12	33m						989		660	329	989	989	958	989		989			Cured
13	32m	869	984				742			984	984	869	984	854	265	854			Cured
14	25m						428	199	358	182	759	143	759	759		616			Cured
15	30m				129	436		129		791	920		919	920	670	920			Cured
16 [*]	28m				732					847	842	847	847	847		727			Cured

ID	Tx	First line Orals			Injectables			Fluoroquinolones			Other Second Line			Other			Outcome		
		EMB	PZA	AMK	CM	KM	SM	CPX	OFX	LFX	MFX	CS	ETH	PAS	AUG	CRT		CFZ	RFB
17	24m					325		84	416	229		730		730	730		730		Cured
18	25m		159	510							756	756		756	597	756	597	159	Cured
19	25m					595				206	744	748	748	748	748		748		Cured
20 ^o	27m		198	434		198		811				811	613	811	632		811		Cured
21	24m				604						729	485	729	729	729		729	122	Cured
22	30m						594				900	900	900	900	900		900		Cured
23	26m	741			547					191	131	791	791	791	322	469	791	469	Cured
24 ^o	31m				565 (565)		565 (565)				948	735	948	948	948	944	948		Cured
25 ^o	28m			861						219	642	861		861	861	861	861		Cured
26	24m				322			244			482	726	613	726	335		335	391	Cured
27 ^o	73m		2227		2227					895	2227	2227		2227	2227		1729		Completed
28	39m				1138			86			1177	1177	86	1177	1177	546	930		Completed
29	30m		344	115	437			276			647	922	578		922		756		Completed
30	12m						352				352	352		352	352	352	352		Died
31	14m	425			425						425	425	425	425	425	425	425	425	Died
32	3m				98					98		98	98	98	98		98		Died

ID	Tx	First line		Injectables						Fluoroquinolones				Other			Outcome		
		EMB	PZA	AMK	CM	KM	SM	CPX	OFX	LFX	MFX	CS	ETH	PAS	AUG	CRT		CFZ	RFB
33	6m						191		191										Died
34	12m					356				356	356								Died
35	11m				348					348	348	348	348	348					Died
36	27m	812	812				812			812	812		785	812			799		Died
37 ^a	13m				387					387	387		387	387	387	387	387	387	Died
38 ⁺	14m				399			301			385	325	419	296			347		Died
39	15m		442	442 (442)	221 (222)	221 (222)			243		199	436	199	442	442	442	442		Died
40	1m																		Died
41 ^a	58m				313		716			313	1446	1720	1720	1759	1759	1446	1194		Failed
42	10m				298				298	298	298		298	298	298	298	298		Failed
43	19m						559			574		574	574	574	574	574	574		Failed
44	13m						385			385	385		385	385	385	385	385		Failed
45	10m				297			244			53	266	213	297	297	297	297		Failed
46	9m		267	267						267	267	267	267	267	267	267	267		Defaulted
47	24m		725	246 (62)	267 (62)					725	725	267	725	725	725	725	725		Defaulted
48	13m	281			380					380	380	380	380	380	380	99	380		Defaulted

Legend for Table 3.

Abbreviations: ethambutol (EMB), pyrazinamide (PZA), amikacin (AMK), streptomycin (SM), kanamycin (KM), capreomycin (CM), ciprofloxacin (CPX), ofloxacin (OFX), gatifloxacin (GFX), levofloxacin (LFX), moxifloxacin (MFX), cycloserine (CS), ethionamide (ETH), para-aminosalicylic acid (PAS), amoxicillin-clavulanic acid (AUG), clarithromycin (CRT), clofazimine (CFZ), rifabutin (RFB)

The column header indicates all the drugs that were considered for inclusion in an individualized regimen.

Each cell corresponds to a specific drug and contains information about:

(a) laboratory-confirmed susceptibility to that drug in any TB isolate collected at the initiation of the individualized regimen (defined as no later than 30 days after the initiation of the individualized regimen and any time prior to that date);

(b) exposure to that drug prior to the individualized regimen, and

(c) administration of that drug during the individualized regimen.



A hash mark in the upper-left quadrant represents confirmed susceptibility in all isolates tested for susceptibility to that drug at the initiation of the individualized regimen.



A filled triangle in the upper-left quadrant indicates that resistance to that drug was demonstrated in at least one isolate collected at the initiation of the individualized regimen.



A blank upper-left quadrant indicates that no susceptibility test results for that drug were available for specimens collected at the initiation of the individualized regimen.



A filled triangle in the upper-right quadrant indicates the subject received that drug for at least 30 days prior to the individualized regimen.



A blank upper-right quadrant indicates the subject received that drug for 0-29 days prior to the individualized regimen.

The large number in a cell indicates the duration in days that the drug was received during the individualized regimen.

In a few cells, there is also a smaller number that appears in parentheses. This indicates the duration in days that this injectable was received simultaneously with any other injectable.

+ Received RIF during the individualized regimen

***** Received INH (900 mg per day) during the individualized regimen

S This patient received sparfloxacin for 368 days

Q Indicates that patient received surgery during the individualized regimen