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NATIONAL
TUBERCULOSIS
CENTER

Medical Management of Tuberculosis

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Introduction



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- About the drugs
- The basic regimen
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General Principles

1. Always treat with a multiple drug regimen
2. Never add a single drug to a failing regimen
3. Determine the duration of therapy based on the drugs used, clinical response, and extent of disease
4. Use isoniazid (INH), rifampin (RIF), pyrazinamide (PZA), & ethambutol (EMB) together—these drugs are the basis of modern short-course (6-month) therapy
5. Consider directly observed therapy (DOT) for all patients

About the Drugs: Isoniazid

■ Isoniazid (INH)

- Good killing of actively dividing organisms
- Documented efficacy in the latent stage



About the Drugs: Rifampin

■ Rifampin (RIF)

- Excellent intracellular killing both active and quiescent organisms
- Required to shorten therapy to <12 months
- Increasing evidence for efficacy in the latent stage



About the Drugs: Pyrazinamide

■ Pyrazinamide (PZA)

- Good killing of actively dividing organisms in an acidic environment
- Decreasing effect after first 2 months of therapy
- Required to shorten therapy to 6 months



About the Drugs: Ethambutol

■ Ethambutol (EMB)

- Bacteriostatic only
- Provides extra agent in case of resistance



The Basic Regimen

- INH and RIF resistance rates are increasing: INH resistance in California is > 9% (as high as 33%)
- 4 drugs, 6 months: unless full susceptibility is known, always add a fourth drug to INH, RIF, and PZA
- Consider DOT for all patients

Initial Phase: First 2 Months (1)

■ Drugs

- INH 300 mg po q day
- RIF 600 mg po q day
(450 mg if < 50 kg)
- PZA 25 mg/kg po q day
- EMB 15 mg/kg po q day



Initial Phase: First 2 Months (2)

■ Dosing and schedule

- All drugs should be taken once daily
- Divided and/or decreased doses are indicated only in special circumstances
- Patients not on DOT should receive fixed dose combination therapy

Continuation Phase: Last 4 Months

- Always check drug susceptibility results

- If fully susceptible:

- INH 300 mg po q day PLUS

- RIF 600 mg po q day

OR

- INH 900 mg po biw PLUS

- RIF 600 mg po biw



- Use DOT for everyone on intermittent therapy

Alternative Regimens

- Cavitation on initial chest X-ray (CXR) or
- Slow responder with culture positive after 2 months of therapy
 - Continue Rx
 - For a total of 9–12 months (i.e., a 7-month continuation phase)
 - OR**
 - For 6 months after culture conversion

Alternative Regimens (2)

- For central nervous system TB
 - Treat for 9–12 months



Alternative Regimens (3)

- When the patient has HIV infection
 - 6 months of therapy is usually adequate
 - Low threshold to prolong therapy to 9–12 months
 - The following are NOT recommended:
 - Biweekly therapy
 - Rifapentine (RPT) regimens

Regimen 1

INITIAL PHASE		CONTINUATION PHASE		Total Duration and Doses (<i>minimum duration</i>)
<i>Drugs</i>	<i>Interval and Doses Minimum Duration</i>	<i>Drugs</i>	<i>Interval and Doses Minimum Duration</i>	
Regimen 1				
Isoniazid Rifampin Pyrazinamide Ethambutol	7 days/week 56 doses (8 wks)	Isoniazid/ Rifampin	7 days/week 126 doses (18 wks)	182 (26 wks)
		Isoniazid/ Rifampin	2 days/week 36 doses (18 wks)	92 (26 wks)
		Isoniazid/ Rifapentine	1 day/week 18 doses (18 wks)	74 (26 wks)

These slides are intended to be examples of how the treatment guidelines are written. They are not comprehensive and not intended to be used to direct treatment. To guide treatment, please see the CDC's Treatment of Tuberculosis, MMWR 2003; 52 (No. RR-11).

Regimen 2

INITIAL PHASE		CONTINUATION PHASE		Total Duration and Doses (<i>minimum duration</i>)
<i>Drugs</i>	<i>Interval and Doses Minimum Duration</i>	<i>Drugs</i>	<i>Interval and Doses Minimum Duration</i>	
Regimen 2				
Isoniazid Rifampin Pyrazinamide Ethambutol	7 days/week 14 doses (2 weeks) THEN 2 days/week 12 doses (6 weeks)	Isoniazid/ Rifampin Isoniazid/ Rifapentine	3 days/week 36 doses (18 wks) 1 day/week 18 doses (18 wks)	62 (26 wks) 44 (26 wks)

Please note that the CDC treatment guidelines recommend a 2 days/week interval for isoniazid/rifampin during the continuation phase. To guide treatment, please see the CDC's Treatment of Tuberculosis, MMWR 2003; 52 (No. RR-11).

Regimen 3-4

INITIAL PHASE		CONTINUATION PHASE		Total Duration & Doses
<i>Drugs</i>	<i>Interval and Doses Minimum Duration</i>	<i>Drugs</i>	<i>Interval and Doses Minimum Duration</i>	<i>(minimum duration)</i>
Regimen 3				
Isoniazid Rifampin Pyrazinamide Ethambutol	3 days/week 24 doses (8 wks)	Isoniazid/ Rifampin	3 days/week 54 doses (18 wks)	78 (26 wks)
Regimen 4				
Isoniazid Rifampin Ethambutol	7 days/week 56 doses (8 wks)	Isoniazid/ Rifampin	7 days/week 196 doses (28 wks)	252 (36 wks)
		Isoniazid/ Rifampin	2 days/week 56 doses (28 wks)	112 (36 wks)

Please note that the CDC treatment guidelines recommend 31 weeks for the Regimen 4 continuation phase. To guide treatment, please see the CDC's Treatment of Tuberculosis, MMWR 2003; 52 (No. RR-11).

Treatment of Drug Resistant Disease

Pattern of Drug Resistance	Suggested Regimen	Duration of Rx
INH (\pm SM)	RIF, PZA, EMB or RIF, PZA, I.A. \pm FQN	6 months
INH and RIF (\pm SM)	FQN, PZA, EMB, I.A., \pm alternative agent	18 to 24 months
INH, RIF, (\pm SM) and EMB or PZA	FQN (EMB or PZA if active) I.A. and two alternative agents	24 months
RIF	INH, PZA, EMB, FQN, \pm I.A.	9 to 12 months
RIF	INH, PZA (for 2 months), EMB	18 months

FQN = fluoroquinolone; most experience involves ofloxacin, levofloxacin, or ciprofloxacin.

I.A. = Injectable agent; may include aminoglycosides (streptomycin, amikacin, or kanamycin) or the polypeptide, capreomycin.

Alternative agents: Ethionamide, cycloserine, para-aminosalicylic acid, clarithromycin, amoxicillin/clavulanate, linezolid.

Extrapulmonary Tuberculosis

■ Duration of therapy

- Lymphadenitis/scrofula: duration of therapy depends on clinical response. Patients may develop new nodes while on therapy, and surgical debulking may be necessary.
- Most extrapulmonary TB: 6 months probably adequate
- Central nervous system TB: 9–12 months

■ Use adjunctive corticosteroids

- Pericardial TB
- Central nervous system TB

Adverse Reactions

■ Most common side effects

- Rash—any agent
- GI intolerance—any agent
- Liver toxicity—INH, RIF, PZA
- Peripheral Neuropathy—INH
- Optic Neuritis—EMB, INH (rare)
- Gout—PZA

Adverse Reactions: Rash

■ Rash

- Any agent—no one knows *a priori* which is the etiologic agent
- If causing only minor itching: antihistamines may be prescribed and TB medications continued
- Petechial rash suggests thrombocytopenia: check platelets; if low, assume RIF hypersensitivity and d/c RIF

Adverse Reactions: Rash (2)

■ Generalized erythematous rash

- Stop all drugs immediately (if acutely ill with TB, may consider 3 alternative drugs)
- When rash has improved significantly, begin rechallenge
 - One drug at a time at 2–3 day intervals
 - Start with INH (or INH plus EMB) then RIF, EMB, and PZA
- If rash recurs, the last drug added is the likely cause and should be discontinued

Adverse Reactions: GI

■ Gastrointestinal intolerance (GI)

- GI includes nausea, vomiting, poor appetite, abdominal pain
- GI symptoms are common, may be transient, and are caused by many anti-TB drugs, particularly in first few weeks
- First, you must rule out hepatitis (ALT/AST)
- If there is no hepatitis, consider:
 - Changing the hour of drug administration
 - Administering drugs with food
 - Taking drugs at bedtime (not if on DOT)

Adverse Reactions: Hepatitis

■ Hepatitis

- Asymptomatic elevation AST/ALT occurs in 20% of patients on 4 drugs
- Drug induced hepatitis is
 - \uparrow AST or ALT ≥ 3 times upper limits of normal in the presence of symptoms **OR**
 - $\uparrow > 5$ times if asymptomatic
- INH, PZA, and RIF can all cause toxicity
 - INH: age related
 - PZA: dose related
 - RIF: idiosyncratic and less common

Adverse Reactions: Hepatitis (2)

■ Hepatitis (continued)

- If asymptomatic, do NOT alter therapy if increase in LFTs is less than 5 times the upper limit of normal
 - ↑ frequency of monitoring
- If symptomatic hold medications if LFTs are 3 or more times higher than the upper limit of normal.

Adverse Reactions:Hepatitis (3)

■ Hepatitis (continued)

□ If $\uparrow \geq 3$ with symptoms **OR** > 5 without symptoms:

- Expert consultation
- Stop all anti-TB medications and evaluate patient
- Order serologic tests for hepatitis A, B, and C
- If severely ill, start 3 non-hepatotoxic drugs
- Rechallenge drugs (starting with INH) one-by-one at weekly intervals after $AST < 2$ times upper limit of normal

Monitoring Therapy (1)

■ Baseline evaluation

- Medical evaluation
- Symptom review
- Laboratory testing (e.g., CBC, electrolytes, BUN, creatinine, LFTs, and uric acid)

■ Face-to-face monthly evaluation

- Medical evaluation
- Symptom review
- Additional laboratory testing as indicated by patient's medical condition

Monitoring Therapy (2)

■ Sputum smears

- Until sustained conversion to negative
- Frequency depends on patient situation

■ Sputum cultures

- Monthly until consistently negative
- Knowing time to culture conversion necessary for determining duration of therapy

Monitoring Therapy (3)

■ Chest x-ray (CXR)

- Baseline for all TB patients
- Consider every 3–6 months during treatment
- Repeat CXR at end of therapy



■ Visual acuity and color discrimination while on EMB

- Baseline
- Monthly

Post-Treatment Monitoring

- Drug-sensitive disease
 - Symptom review
 - Medical evaluation for a minimum of 6 months after completion
- MDR-TB, recurrent TB, extensive disease, or poor adherence to treatment
 - More intensive end-of-treatment and post treatment monitoring
 - MDR-TB indefinite monitoring

Conclusion

- In this presentation, we've covered:
 - The essential principles of TB care
 - The 4 drugs that are the mainstays of TB treatment
 - Adverse reactions associated with these drugs
 - Monitoring of patients throughout therapy
- Please review the supplemental materials
- Thank you!

