

Medical & Case Management of Drug-Susceptible TB

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Learning Objectives

By the end of this training, participants will be able to:

1. identify the recommended regimens and first-line medications for treating drug-susceptible TB disease
2. state several criteria for when treatment for drug-susceptible TB should be extended to at least 9 months
3. describe common side effects and the associated monitoring required for individual first-line anti-TB drugs
4. describe the key components of TB case management
5. identify the baseline evaluations that should be obtained prior to starting treatment for drug-susceptible TB disease
6. monitor and document clinical findings to evaluate for response to TB treatment



Poll Question 1

How many patients with TB disease have you managed to date?

- a) None
- b) 1-5
- c) 6-10
- d) >10



EXPOSED Chapter 1 : The Global Epidemic



Overview Case Management, TB Treatment Regimens, and Duration

Case Management Definition

“Case Management is a collaborative process of assessment, planning, facilitation, care coordination, evaluation and advocacy for options and services to meet an individual’s and family’s comprehensive health needs through communication and available resources to promote patient safety, quality of care, and cost effective outcomes.”

~Case Management Society of America



Poll Question 2

When a person with TB is reported to the public health department, who is ultimately responsible for ensuring that the patient is evaluated and, if necessary, completes TB treatment?

- a) The treating physician
- b) The public health department case manager
- c) The outreach worker who delivers the medications
- d) The patient
- e) I don't know yet



Case Management Definition

The Nurse Case Manager (NCM) is accountable to the patient and is responsible for leading the following activities:

- Setting goals
- Providing education, medication, and medical monitoring
- Coordinating care
- Documenting interventions
- Ensure completion of treatment
- Leading the Contact Investigation
- Evaluate and document clinical response to treatment



Goals of TB Treatment

- Individual patient
 - Prevent the health consequences of untreated TB
 - Avoid severe or intolerable adverse effects of TB treatment
- Public health goals
 - Stop transmission of TB to contacts and the community
 - Prevent the development of acquired drug-resistance by *Mycobacterium tuberculosis*



Poll Question 3

If all medications are taken on schedule, generally how long is the initial phase of treatment for drug-susceptible pulmonary TB?

- a) 1 month
- b) 2 months
- c) 3 months
- d) 4 months
- e) I don't know yet



General Principles Pan-Susceptible

- Initial Phase (initial 2 months of treatment)
 - Prevents drug resistance until drug susceptibility testing (DST) is known and increases ability to shorten treatment
- Continuation Phase (subsequent 4-7 months of treatment)



- Duration of therapy (or number of doses needed) is dependent on:
 - Drugs used
 - Extent of disease
 - Response to treatment
 - Co-morbidities (e.g. HIV, immune-compromise)

Treatment for Drug-Susceptible TB

Initial Phase (2-complete months)

- Rifampin
- Isoniazid
- Pyrazinamide
- Ethambutol
 - EMB can be dropped once confirmed susceptible
- Vitamin B6 50mg

Continuation Phase (4-7 months)

- Rifampin
- Isoniazid
- Vitamin B6 50mg



Medications (Pan-Susceptible)

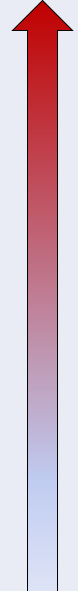
- Rifampin (RIF, “R”), 10 mg/kg/d
- Isoniazid (INH, “H”), 5 mg/kg/d
- Pyrazinamide (PZA, “Z”), 25 mg/kg/d
- Ethambutol (EMB, “E”), 15-25 mg/kg/d





<https://www.currytbcenter.ucsf.edu/products/view/rifamycin-drugdrug-interactions-a-guide-for-primary-care-providers-treating-latent-tuberculosis>

Regimens for Drug-susceptible TB

Regimen	INTENSIVE PHASE		CONTINUATION PHASE		Range of total doses	Comments ^{3, 4}	Regimen effectiveness
	Drugs ¹	Interval and Dose ² (Minimum Duration)	Drugs	Interval and Dose ^{2,3} (Minimum Duration)			
1	INH RIF PZA EMB	7 days/week for 56 doses (8 wks) OR 5 days/week for 40 doses (8 wks)	INH RIF	7 days/week for 126 doses (18 weeks), OR 5 days/week for 90 doses (18 weeks)	182 to 130	This is the preferred regimen for patients with newly diagnosed pulmonary tuberculosis.	 <p>Greater</p> <p>Lesser</p>
2	INH RIF PZA EMB	7 days/week for 56 doses (8 wks) OR 5 days/week for 40 doses (8 wks)	INH RIF	3 times weekly for 54 doses (18 weeks)	110 to 94	Preferred alternative regimen in situations in which more frequent DOT during continuation phase is difficult to achieve.	
3	INH RIF PZA EMB	3 x/week for 24 doses (8 wks)	INH RIF	3 times weekly for 54 doses (18 weeks)	78	Use regimen with caution in patients with HIV and/or cavitary disease. Missed doses can lead to treatment failure, relapse, and acquired drug resistance.	
4	INH RIF PZA EMB	7 days/week for 14 doses THEN 2 x/week for 12 doses ⁵	INH RIF	Twice weekly for 36 doses (18 weeks)	62	Do not use 2x/weekly regimens in HIV-infected patients or patients with smear-positive and/or cavitary disease. If doses are missed, then therapy is equivalent to once weekly, which is inferior.	

Source: Adapted from 2016 ATS/CDC/IDSA Clinical Practice Guidelines: Treatment of Drug-susceptible Tuberculosis, Table 2



For presumed DS-PTB, continuation phase generally extended when...

Cavitary disease on chest X-ray	Sputum Culture Positive after 2-months treatment	Co-Morbidity or extensive PTB disease	PZA Received for 8-full weeks	Continuation Phase: Extend to 7 months
No	No	No	No	Yes
Yes	Yes	No	Yes	Yes
Yes	No	Yes	Yes	Yes
No	Yes	Yes	Yes	Yes

- Initial phase excluded or had insufficient duration of PZA

Continuation phase generally extended when...

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- Initial phase excluded or had insufficient duration of PZA
- Cavitary disease and sputum culture (+) at 2M¹ (~ 20% relapse with 6M course)

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Yes	No	+	Yes	Yes
No	Yes	+	Yes	Yes

- Initial phase excluded or had insufficient duration of PZA
- Cavitary disease and sputum culture (+) at 2M¹ (~ 20% relapse with 6M course)
- If cavitary or sputum positive extend if:
 - Lower than 10% ideal body weight (BMI of <18)
 - Active smoker
 - Diabetes, HIV infection, or any other immunosuppressing condition
 - Extensive disease on chest radiograph

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 - Extensive disease on chest radiograph
- Silicotuberculosis² (longer duration decreased relapses from 22% to 7%)

1 Jo KW, Yoo JW, Hong Y, et al. Risk factors for 1-year relapse of pulmonary tuberculosis treated with a 6-month daily regimen. *Respir Med* 2014; 108:654–9.

2 Hong Kong Chest Service/Tuberculosis Research Centre, Madras/British Medical Research Council A controlled clinical comparison of 6 and 8 months of anti-tuberculosis chemotherapy in the treatment of patients with silicotuberculosis in Hong Kong. *Am Rev Respir Dis*. 1991;143:262–267.



NEW 4 MONTH REGIMEN: HPMZ

ORIGINAL ARTICLE

Four-Month Rifapentine Regimens with or without Moxifloxacin for Tuberculosis

S.E. Dorman, P. Nahid, E.V. Kurbatova, P.P.J. Phillips, K. Bryant, K.E. Dooley, M. Engle, S.V. Goldberg, H.T.T. Phan, J. Hakim, J.L. Johnson, M. Lourens, N.A. Martinson, G. Muzanyi, K. Narunsky, S. Nerette, N.V. Nguyen, T.H. Pham, S. Pierre, A.E. Purfield, W. Samaneka, R.M. Savic, I. Sanne, N.A. Scott, J. Shenje, E. Sizemore, A. Vernon, Z. Waja, M. Weiner, S. Swindells, and R.E. Chaisson, for the AIDS Clinical Trials Group and the Tuberculosis Trials Consortium

Slow Local Adoption

- Logistical concerns:
 - Up front molecular DST for MFX not available
 - Rifapentine shortage
 - ECGs
 - Cost
- Efficacy concerns
- Tolerability concerns (Baggio & Ananda-Rajah, 2021)
 - QT prolongation and cardiac arrhythmia
 - Tendon rupture, muscle pain, long term pain
 - Retinal detachment
 - Nausea, vomiting, diarrhea and taste disturbance (20% of patients)
 - Risk of c.diff
 - Hyperglycemia and hypoglycemia

Management of Treatment Interruptions

Time Point of Interruption	Details of interruption	Approach
During intensive phase	Lapse is <14 days in duration	Continue treatment to complete planned total number of doses (as long as all doses are completed within 3 months)
	Lapse is ≥ 14 days in duration	Restart treatment from the beginning
During continuation phase	Received ≥ 80% of doses and sputum was acid-fast bacilli (AFB) smear negative on initial testing	Further therapy may not be necessary
	Received ≥ 80% of doses and sputum was AFB smear positive on initial testing	Continue therapy until all doses are completed
	Received <80% of doses and accumulative lapse is <3 months in duration	Continue therapy until all doses are completed (full course), unless consecutive lapse is > 2 months. If treatment cannot be completed within recommended timeframe for regimen, restart therapy from the beginning (i.e., restart intensive phase, to be followed by continuation phase) ^b
	Received <80% of doses and lapse is ≥ 3 months in duration	Restart therapy from the beginning, new intensive and continuation phases (i.e., restart intensive phase, to be followed by continuation phase)

a According to expert opinion, patients who are lost to follow-up (on treatment) and brought back to therapy, with interim treatment interruption, should have sputum resent for AFB smear, culture, and drug susceptibility testing.

b The recommended time frame for regimen, in TB control programs in the U.S. and in several European countries, is to administer all of the specified number of doses for the intensive phase within 3 months and those for the 4-month continuation phase within 6 months, so that the 6-month regimen is completed within 9 months.

Source: Adapted from 2016 ATS/CDC/IDSA Clinical Practice Guidelines: Treatment of Drug-susceptible Tuberculosis, Table 6, New York example



Completion of Therapy

Completion of treatment is primarily defined by the number of ingested doses within a specified time frame.

Completion is not determined only by the number of doses but also the time frame.

Examples:

- 6-month daily regimen (7 days/wk) = at least 182 doses of INH and RIF, and 56 doses of PZA
- 6-month daily regimen (5 days/wk) = at least 130 doses
- Daily dosing is 7 days per week. Complete either 26 weeks or 39 weeks
 - 5 out of 7 days (5/7) can be considered “daily” treatment



Completion of Therapy

Specified doses must be administered

Phase	Treatment Length	Completion Criteria
Initial Phase	2 months	Within 3 months
		Cannot miss more than 2 weeks in initial phase or start over.
Continuation Phase	4 months	Within 6 months
	7 months	Within 9 months

Consider therapy interrupted if target doses not met within specified time period

Break

The 20-20-20 Rule

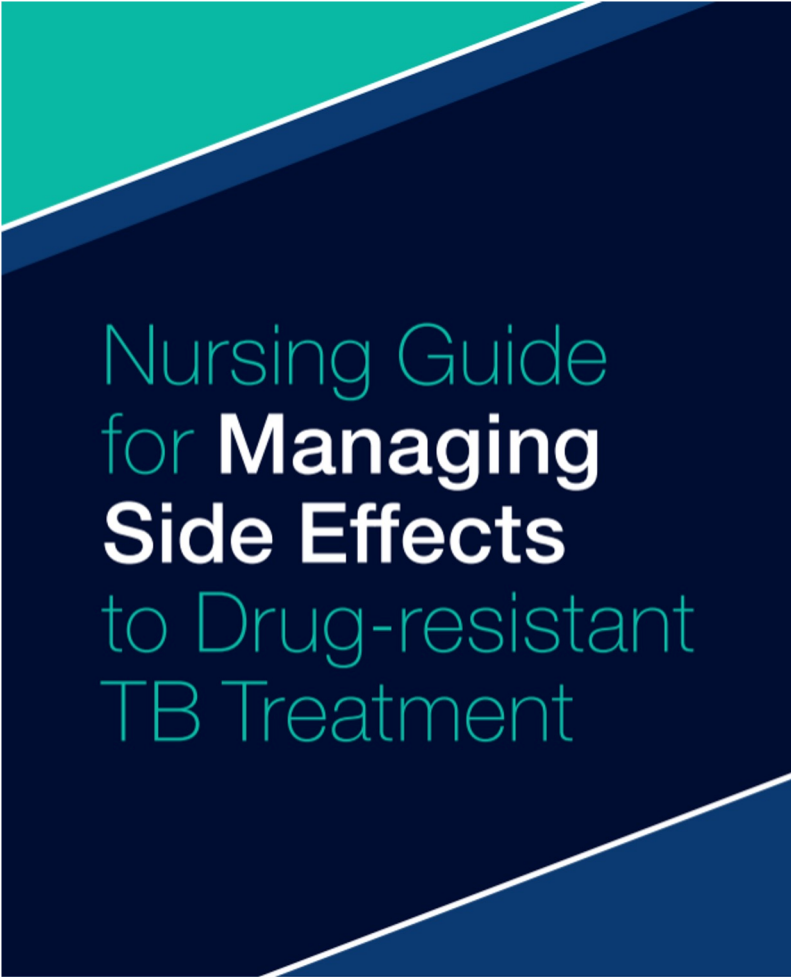
For every 20 minutes spent looking at a screen, a person should look at something 20 feet away for 20 seconds



Adverse Reactions, Drug Interaction, Treatment Failure and Relapse



Adverse Reactions



Adverse Reactions: First-Line Drugs

Drug / daily dose	Hepatotoxicity	Specific adverse	Additional
Rifampin, 10mg/kg (max: 600 mg)	+	Rash, pruritus, hypersensitivity GI upset Thrombocytopenia Hemolytic anemia	Speeds metabolism of many drugs (consider drug-drug interactions)
INH, 5 mg/kg (max: 300 mg)	++	Peripheral neuropathy Drug-induced lupus CNS symptoms Optic neuritis	Co-administer with B6
PZA, 25 mg/kg	++	Gout Hyperuricemia Arthralgias Photosensitivity	Dose adjustment to TIW in CrCl<30 Dose after hemodialysis
EMB, 15-25 mg/kg		Retrobulbar neuritis (dose-related, exacerbated by chronic kidney disease)	Use higher dose only during initial months. Dose adjustment to TIW in CrCl<30 Dose after hemodialysis

Adverse Reactions: Second-Line Drugs (commonly used)

Drug / daily dose	Hepatotoxicity	Specific adverse	Additional
Rifabutin, 5 mg/kg (max: 300 mg)	+	Anterior uveitis Leukopenia Thrombocytopenia Arthralgias	<20% of rifampin-resistant strains will have in vitro susceptibility to RFB
Moxifloxacin, 400mg	Rare	QTc prolongation Tendon rupture GI upset C diff risk	
Levofloxacin, 750mg (typically)		QTc prolongation Tendon rupture GI upset C diff risk	Dose adjustment to TIW in CrCl<30

Drug Interactions

- Relatively few drug interactions substantially change concentrations of anti-tuberculosis drugs
- Anti-tuberculosis drugs sometimes change concentrations of other drugs:
 - Rifamycins can decrease serum concentrations of many drugs, (e.g., most of the HIV-1 protease inhibitors, hormonal birth control), to sub-therapeutic levels
 - Isoniazid increases concentrations of some drugs (e.g., phenytoin) to toxic levels

Treatment Failure

- Defined as positive cultures after 4 months of treatment in patients for whom medication ingestion was ensured
- Single new drug should **NEVER** be added to a failing regimen; it may lead to acquired resistance to the added drug
- Add at least three new drugs to the existing regimen being cognizant of the possibility of drug resistance
- Encourage ongoing consultation through State TB Program



Treatment Failure

- Red flags-
 - Delayed culture conversion (i.e. > 60 days); may need to use smears as surrogate while awaiting cultures
 - Worsening imaging at 2 months
 - Worsening or persistent symptoms at 2 months
- At risk – large burden of disease, cavitary, diabetic
- Recommendations-
 - Determine if development of resistance has occurred (repeat DST, molecular testing) and if regimen needs to be expanded
 - Assess if malabsorption present
 - Assess adherence
 - Check drug levels (TDM)



Relapse

- A patient's cultures become and remain negative while receiving anti-tuberculosis drugs, but at some point after completion of therapy:
 - Patient develops culture-positive TB disease again
- OR
- Patient experiences clinical or radiographic deterioration consistent with active TB disease



Relapse

Most relapses occur within the first 12 months after completion of therapy.

- Patients who had cavitation on initial CXR and a positive culture at completion of 2 months of therapy are at an increased risk of relapse with standard 6-month regimens.
- Other factors that make relapse more likely:
 - Cavitory disease or sputum positive
 - Extensive Disease
 - Lower than 10% ideal body weight
 - Active smoker
 - Diabetes, HIV infection, or any other immunosuppressing condition
 - Extensive disease on chest radiograph
- Patients with relapse are at an increased risk for acquired drug resistance, especially if the therapy was not directly observed



Respond in the Chat:

What are the steps of TB case management?



Case Management Fundamentals



Steps of Case Management

- Steps in TB case management:
 - Establish rapport/Provide education
 - Stop transmission/Start medications
 - Home assessment/Contact investigation



Key Components

- Assess current status of the client
 - Medical/Physical
 - Psychological
 - Financial
 - Social
 - Cultural
- Holistic care





Key Components of TB Case Management

- Initial Review:
- Review and discuss any problems or concerns
 - Is more clinical information needed?
 - Is the patient infectious? Is isolation needed?
 - Are there any other medical/social problems that need to be addressed?
 - Is the treatment regimen appropriate based on ATS/CDC Guidelines?
 - Is an interpreter needed?
 - Is the home safe for the patient and inhabitants?
 - Are there outreach workers who will be seeing the patient?



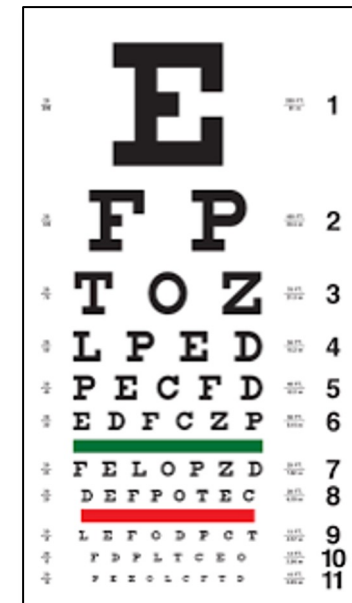
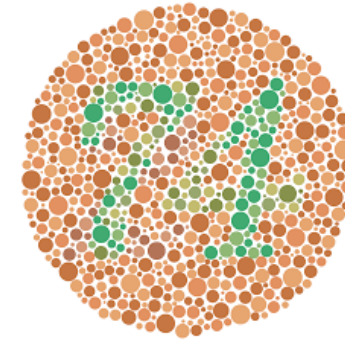
Baseline Evaluation and Monitoring



Baseline Evaluation

History and Physical

- Medication review
- Weight and Height (BMI)
- Imaging (CXR for pulmonary, may be other imaging for extra-pulmonary)
- CBC and CMP
- HIV screening
- Hepatitis B/C screening
 - For IVDU, foreign-born Asia/Africa
- Visual acuity, red-green color discrimination
 - Ishihara and Snellen



Clinical Monitoring

- Daily
 - Adherence (DOT)
 - Symptom review
- Monthly (and prn)
 - Face-to-face symptom review by RN
 - Visual acuity, color discrimination (if on EMB)
 - Weight: re-dose medications as needed
- CXR (for pulmonary TB) or other imaging
 - Depends: 2 mo, 6 mo, or end of treatment
- Sputum:
 - Every 2 weeks until culture conversion



Laboratory Monitoring

- Routine lab monitoring is not typically recommended except for those at high-risk or symptomatic
Regardless, clinical monitoring is a MUST!
- LFTs:
 - Underlying hepatic disease
 - Pregnancy or post-partum
 - HIV
 - IVDU or ETOH abuse
 - Consider: Age >50 yo, concomitant hepatotoxic medications
- Creatinine
 - Underlying renal disease
 - PZA, EMB require renal dosing if creatinine clearance <30
- CBC
 - Underlying hematologic abnormality
 - Rifabutin (can cause leukopenia, thrombocytopenia)



Directly Observed Therapy (DOT)



Directly Observed Therapy (DOT)

- Health-care worker watches patient swallow each dose
- DOT is standard of care for all patients who have TB disease
- Can reduce acquired drug resistance, treatment failure, and relapse
- Nearly all regimens can be intermittent if given as DOT
- DOT reduces total number of doses and encounters



DOT/EDOT/VDOT

DOT: Direct Observed Therapy: Traditional form when a patient is watched taking their medication in person

EDOT: Electronic Direct Observed Therapy (EDOT): Patient is observed taking their medication over electronic streaming

VDOT: Video Direct Observed Therapy: Video is recorded and a nurse reviews videos to ensure patient is taking their medication



Diligence

Through the diligence of public health employees, we can eliminate TB!



Break

10 minute break





On March 12, a hospitalist diagnosed Nancy, a 28-year-old Chinese-American female, with pulmonary TB disease. Nancy had the following tests results:

- IGRA: Positive
- Chest X-Ray (CXR): Showed cavities in the right upper lobe
- Sputum Samples: 2 sputum samples were smear positive on AFB smear (4+)
- NAAT: Not ordered
- Cultures: Awaiting results

On the same day the hospital, assuming Nancy had drug-susceptible TB, started her on the following medications:

- Isoniazid (INH) (Daily)
- Ethambutol (BID)
- Rifampin (BID)



The hospital's Infection Preventionist (IP) contacted your Local Public Health Agency (LPHA) on March 20 providing patient information and noting a discharge home on March 15. You are assigned as the case manager on March 22 and you visit Nancy's home on March 30.

When you make your home visit on March 30, you learn that Nancy works for a garment factory as a seamstress. She reports that she has been feeling much better and plans to return to work the following day, indicating that her family needs money for rent.

During your visit you observe that there is very little food in the home and Nancy has a low BMI. Initially, Nancy denies having children, however, you observe that there is a baby sock in the corner and a few scattered toys. After discussion and education, Nancy discloses that she lives with her children (ages 1.5 and 3 years old), as well as her husband, mother, and sister in their 2-bedroom apartment.

You put together the following table to help yourself better understand the timeline and information you have already gathered.



Date	Incident	Notes
March 12 th	Nancy was diagnosed with pulmonary TB disease by a hospitalist.	IGRA: Positive Chest X-Ray (CXR): Showed cavities in the right upper lobe Sputum Samples: 2 sputum samples were smear positive on AFB smear (4+) NAAT: Not ordered Cultures: Awaiting results
March 12 th	The hospitalist initiated treatment for drug-susceptible TB disease.	Isoniazid (INH) (Daily) Ethambutol (BID) Rifampin (BID)
March 15 th	Nancy was discharged from the hospital to her home.	
March 20 th	The Hospital IP contacted your LPHA to report TB disease.	
March 22 nd	You are assigned to be Nancy's case manager.	
March 30 th	You visit Nancy in her home.	<p>During this visit you learn:</p> <p>Nancy works for a garment factory as a seamstress.</p> <p>Nancy plans to return to work tomorrow- if she doesn't return to</p>



1. What are the medical issues in the scenario, and follow up questions to ask?



2. What are the case management issues in the scenario, and follow up questions to ask?



3. What comments do you have about the timeline presented in the scenario?



4. What is your plan for follow-up with the hospitalist and IP?



5. How do you address Nancy's plans to return to work?



6. What are the educational needs for Nancy and her family? Explain how you will provide this education.



Questions?

