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Global Tuberculosis Institute
NEW JERSEY MEDICAL SCHOOL

Treatment of Tuberculosis

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Outline

- Principles of treatment of tuberculosis
- Recommended treatment regimens
- Case management and monitoring
- Special circumstances

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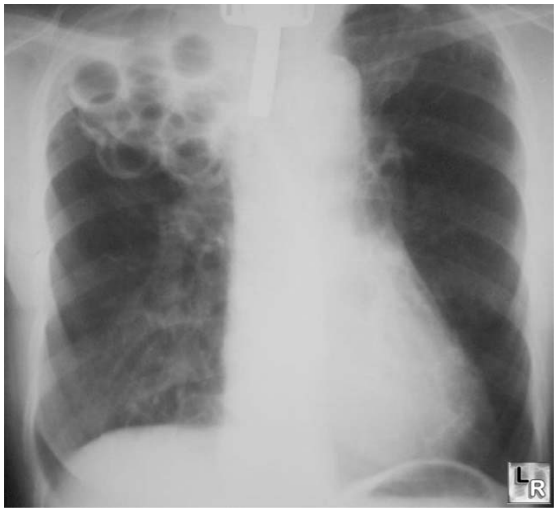
Treatment of Tuberculosis, 1940's



Saskatchewan Lung Association

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Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis

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Replaces CDC: *Treatment of Tuberculosis*, MMWR. June 20, 2003 / Vol. 52 / No. RR-11

* Clin Infect Dis, 2016:63 (1 October) • e147
https://www.cdc.gov/tb/publications/guidelines/pdf/cid_ciw694_full.pdf

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"Evidence-based" Guidelines* for the Treatment of Tuberculosis

Strength of the recommendation

A. Preferred; should generally be offered
B. Alternative; acceptable to offer
C. Offer when *A* or *B* regimens cannot be given
D. Should generally not be offered
E. Should never be offered

Quality of evidence supporting the recommendation

I. At least 1 randomized trial with clinical endpoints
II. Clinical trials that were not randomized or were performed in other populations
III. Expert opinion

* IDSA/USPHS

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Objectives of TB Treatment

The objectives of TB therapy are:

- Cure the individual patient and minimize risk of death and disability
- Reduce transmission of *M. tuberculosis* to other persons
- Prevent the development of drug resistance during therapy

ATS/IDSA/CDC 2016 Treatment Guidelines

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Key Considerations

- Recommendation 1: Patient-centered approach
  - Endorses the use of case management
    - Conditional recommendation; very low certainty of evidence
- Recommendation 2: DOT for all forms of TB disease
  - Conditional recommendation; very low certainty in the evidence

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Goals of Anti-tuberculosis Chemotherapy

- Rapid killing of tubercle bacilli
- Minimize potential for organisms to develop drug resistance: Combination chemotherapy
- Sterilize host tissues: Sufficient length of treatment

Result: Patient is cured with very small likelihood of relapse

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Initiation of Therapy

- Often is based on high index of suspicion
  - Do not delay treatment waiting for smear and culture results, especially in ill and vulnerable patients
  - Absence of AFB on smear or granulomas on biopsy does not rule out tuberculosis, nor does negative TB culture
  - A positive TST or IGRA is only supportive, may be negative in 15-25% of cases

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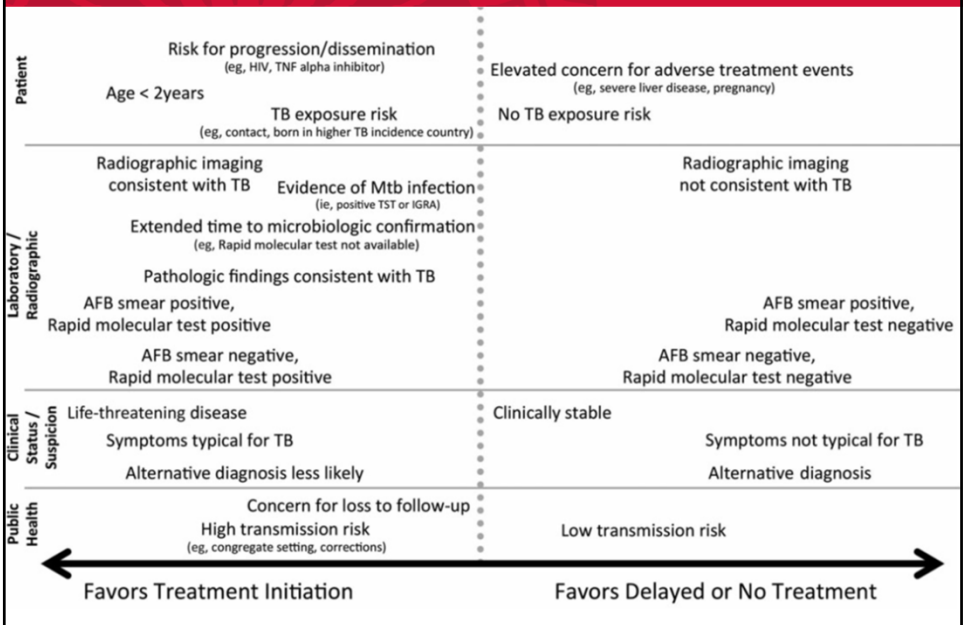
Factors to Consider in Empiric Treatment



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Drugs in Current Use

First-line	Second-line	xxx-line
Isoniazid (INH)	Cycloserine	Linezolid*
Ethambutol (EMB)	Levofloxacin*	Bedaquiline
Rifampin (RIF)	Ethionamide	
Rifabutin* (RBT)	Moxifloxacin*	
Rifapentine (RPT)	*p*-Aminosalicylic acid (PAS)	
Pyrazinamide (PZA)	Capreomycin	
Streptomycin (SM)	Gatifloxacin*	
	Amikacin/Kanamycin*	

** Not approved by FDA for use in tuberculosis*

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Bedaquiline (TMC 207)

- Accelerated FDA approval, November 2012
  - 2 studies involving a total of 440 patients with MDR-TB
  - Safety concerns
- Unique mechanism
  - ATP synthase proton pump inhibitor
- Indication
  - As part of combination therapy for the treatment of MDR pulmonary TB in adults
- Phase 3 trial
  - Double-blind study: 9 months bedaquiline *versus* placebo, with background regimen

Sirturo® Janssen Therapeutics

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Treatment of Culture-positive Pulmonary Tuberculosis

General Conclusions from the Literature

- 26 wks is the minimum duration of treatment
- “6 month” regimens require a rifamycin throughout and PZA for the first 2 months
- “6 month” regimens are effective without INH

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Treatment of Culture-positive Pulmonary Tuberculosis

General Conclusions from the Literature

- Without PZA minimum duration is 9 months (39 wks)
- Without RIF, minimum duration is 12 months (up to 18+ mos)
- SM and EMB are approximately equivalent in effect

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Multiple Drugs?

- Resistance mutations occur spontaneously within a replicating population of bacteria with a predictable frequency (*f*)
  - *f* Rif-R mutation 10^{-8}; INH-R 10^{-6}
- Mutations appear independently of each other
- Among a population of 10^9 AFB (*e.g.,* Intra-cavitary), 10 bacteria will be Rif-resistant; 1,000 will be INH-resistant
  - These resistant populations will be mutually exclusive
  - Therefore 2 drugs will cover the entire population

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Why These Drugs: Objectives of TB Therapy

- Kill actively multiplying bacteria (Initial phase)
  - Improve symptoms & prevent death
  - Prevent transmission to others
  - Prevent emergence of resistance
- Sterilize disease sites (Continuation phase)
  - Cure the disease
- Drugs differ in their activity against TB
  - Bactericidal
  - Bacteriostatic

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Why Do We Use These Drugs?

- Each drug has a special role in TB therapy
  - Isoniazid (H, INH): Early bactericidal activity (kill the dividing bacteria)
  - Rifampin (R, Rif): Sterilizing activity (prevents relapse)
  - Pyrazinamide (Z, PZA): Special 'shortening' activity, sterilizing activity
  - Ethambutol (E, EMB): Fortify the regimen to prevent drug resistance

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Bacterial Targets of TB Therapy

- **Rapidly** multiplying bacteria (in cavities)
- **Slowly** multiplying bacteria (in acidic environment of macrophages or cavity wall)
- **Sporadically** multiplying bacteria (location?)

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Bactericidal

- Ability of drug to rapidly kill multiplying *M. tb*
- Drugs that have early bactericidal activity reduce the chance of resistance developing
  - INH/moxifloxacin > RIF > EMB
  - PZA is poor in this regard
- "Intensive" phase: attempting to rapidly kill multiplying bacteria
  - Smear and culture conversion

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Sterilizing

- Ability of drug to kill bacilli, mainly in the subpopulations of *M. tb,* that persist beyond the early months of therapy
  - RIF (and PZA) have the greatest sterilizing activity
- "Continuation" phase: Attempting to sterilize/cure to prevent relapse

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The Unique Role of PZA

- PZA does not protect against the emergence of resistance in a companion drug
- It is essential in the first 2 months to allow a short course (i.e., 6 month) regimen (BMC trials)
- PZA works best in low pH environments

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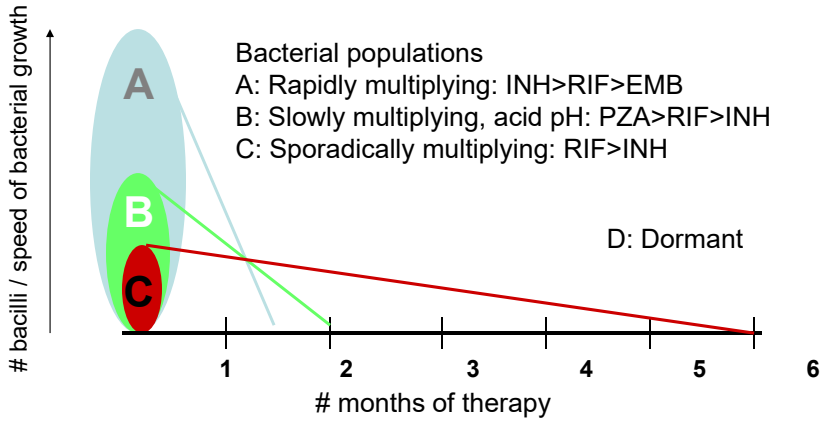
Hypothetical Model of TB Chemotherapy

3 anatomic/metabolic populations of bacilli in cavitary TB



M. Iseman, D. Mitchison

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Preventing Complications: *Drug Selection and Dosing*

- Select individual treatment regimen based on individual risk factors for toxicity, clinical, and life conditions
  - Understand specific toxicities of TB medications
    - *e.g.,* Avoid hepatotoxic medications in patients with active hepatitis
  - Tailor regimen to accommodate lifestyle of patient
    - Case management-DOT → SAT?
- Adjust doses of specific drugs as necessary
  - Use weight-based dosing
  - Reduce doses of specific drugs if metabolism is impaired
    - *e.g.,* Increase dosing interval of EMB in renal failure (3x/wk, with dialysis)
  - Consider drug level testing/monitoring in specific circumstances
    - Malabsorption?

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Recommended Treatment Regimens

- Recommendation 3: Intensive phase
  - Daily dosing preferred
    - Strong recommendation; moderate certainty
  - May consider intermittent therapy (3x/wk)
    - Low risk for relapse
    - HIV neg
      - Conditional recommendation; low certainty
- Recommendation 4: Continuation phase
  - Daily dosing or 3x/wk
    - Strong recommendation; moderate certainty
  - Avoid 2x/wk regimens if possible
  - Avoid use of 900 INH/900 RPT 1x/wk
    - Strong recommendation; high certainty

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Table 2. Drug Regimens for Microbiologically Confirmed Pulmonary Tuberculosis Caused by Drug-Susceptible Organisms

	Intensive Phase		Continuation Phase				
Regimen	Drug[a]	Interval and Dose[b] (Minimum Duration)	Drugs	Interval and Dose[b,c] (Minimum Duration)	Range of Total Doses	Comments[c,d]	Regimen Effectiveness
1	INH RIF PZA EMB	7 d/wk for 56 doses (8 wk), or 5 d/wk for 40 doses (8 wk)	INH RIF	7 d/wk for 126 doses (18 wk), or 5 d/wk for 90 doses (18 wk)	182–130	This is the preferred regimen for patients with newly diagnosed pulmonary tuberculosis.	Greater
2	INH RIF PZA EMB	7 d/wk for 56 doses (8 wk), or 5 d/wk for 40 doses (8 wk)	INH RIF	3 times weekly for 54 doses (18 wk)	110–94	Preferred alternative regimen in situations in which more frequent DOT during continuation phase is difficult to achieve.	
3	INH RIF PZA EMB	3 times weekly for 24 doses (8 wk)	INH RIF	3 times weekly for 54 doses (18 wk)	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 d/wk for 14 doses then twice weekly for 12 doses[e]	INH RIF	Twice weekly for 36 doses (18 wk)	62	Do not use twice-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.	Lesser

Abbreviations: DOT, directly observed therapy; EMB, ethambutol; HIV, human immunodeficiency virus; INH, isoniazid; PZA, pyrazinamide; RIF, rifampin.

[a] Other combinations may be appropriate in certain circumstances; additional details are provided in the section "Recommended Treatment Regimens."

[b] When DOT is used, drugs may be given 5 days per week and the necessary number of doses adjusted accordingly. Although there are no studies that compare 5 with 7 daily doses, extensive experience indicates this would be an effective practice. DOT should be used when drugs are administered <7 days per week.

[c] Based on expert opinion, patients with cavitation on initial chest radiograph and positive cultures at completion of 2 months of therapy should receive a 7-month (31-week) continuation phase.

[d] Pyridoxine (vitamin B6), 25–50 mg/day, is given with INH to all persons at risk of neuropathy (eg, pregnant women; breastfeeding infants; persons with HIV; patients with diabetes, alcoholism, malnutrition, or chronic renal failure; or patients with advanced age). For patients with peripheral neuropathy, experts recommend increasing pyridoxine dose to 100 mg/day.

[e] See [426]. Alternatively, some US tuberculosis control programs have administered intensive-phase regimens 5 days per week for 15 doses (3 weeks), then twice weekly for 12 doses.

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Treatment of Culture-positive Pulmonary Tuberculosis

Preferred Regimen

2 mos - I, R, Z, E daily (56 doses, 8 wks) ***then***

4 mos - I, R daily (126 doses, 18 wks) ***or***

4 mos - I, R 3X / wk (56 doses, 18 wks)

Continuation phase increased to 7 months if initial film shows cavities and sputum is culture-positive at completion of 2 months of treatment ("Expert Opinion")

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Tailoring Tuberculosis Treatment Regimens

Rationale for Extending Treatment by 3 Months

- Continuation of PZA for additional 2 months does not improve outcome
- Prolongation of continuation phase by 2 months decreased relapses in silico-tuberculosis from 20% to 3%

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Risk Factors for Relapse: Study 22

Continuation Phase, Control (I/R Twice weekly)

Cavity	Culture Positive at 2 Mos	
	Yes	No
Yes	**21.8%**	6.2%
No	5.0%	**2.1%**

Tuberculosis Trials Consortium. Lancet. 2002; 360: 528

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Sputum Monitoring

- Obtain sputum every month until culture-negative for at least 2 consecutive months
- For those with *either* delayed culture conversion (beyond 2 months) *or* cavitation on plain CXR, clinicians may extend treatment to 9 months, although 6 mos is acceptable
- For those with *both* cavitation and delayed culture conversion, 9 months is recommended
- Patients with sputum cultures that remain positive at 3 months require further investigation

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Baseline Evaluations

- Collect appropriate specimens for microscopy and culture
  - 3 sputum samples, *8-24 hr apart*
  - Sputum induction or bronchoscopy
- Perform susceptibility testing for INH, Rif, EMB on an initial positive culture (each site of disease)
- Perform HIV counseling and testing for *all* patients/suspects
  - CD4, viral load if HIV-positive

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Monitoring for Drug Toxicity

- At baseline
  - ALT, bilirubin, alkaline phos., serum creatinine, and platelet count
  - Eye examination (V_a, color) for all patients receiving EMB
  - Education!
- At least MONTHLY
  - Clinical evaluations usually are sufficient, *unless* abnormal baseline values are found or other risk factors for toxicity exist
    - *e.g.,* Risk factors for hepatitis: chronic hepatitis (hep. C), use of hepatotoxic drugs (including acetaminophen, EtOH, ?lipid lowering drugs), age (>35), postpartum, young black or Hispanic women
  - Eye examinations (EMB) – Monthly testing of V_a and color is recommended for patients receiving EMB >15-20 mg/kg/d and if on drug for >2 mos
- For 2nd and 3rd-line medications, seek expert consultation

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Response to Treatment

- May be rapid (days)
  - Signs/symptoms
- Expect > 90% sputum culture conversion by 3 months
  - If slow conversion – evaluate and consider longer treatment
- Allow return to home/work environment based on individual considerations
  - Infectiousness of case (look for clinical response, declining organisms on smear)
  - Risk of others becoming infected (contacts)

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Follow-up Evaluations

- For pulmonary TB
  - Sputum smear/culture monthly until 2 consecutive samples are culture negative
    - Repeat drug susceptibility testing, other investigations, if culture-positive still at 3 months
  - If initial culture positive - consider repeat CXR at 2 mos, and get CXR at completion of therapy
  - If initial culture negative – perform 2 mos CXR to assess response; CXR at completion of therapy
- For extra-pulmonary TB
  - Frequency and types of evaluations depend on site

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Clinical Hepatitis in Persons Taking INH & RIF

Drug	Studies	Patients	% Clinical Hepatitis
INH	6	38,257	0.6
INH + other drugs (*NOT* Rif)	10	2,053	1.6
INH + Rif	19	6,155	2.7
Rif + other drugs (*NOT* INH)	5	1,264	1.1

Steele, *et. al*. Chest 99: 465 – 471, 1991

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Serum Drug Level Monitoring

- Useful in selected circumstances
  - *e.g.,* Inadequate response to treatment, severe disease where malabsorption is questioned
- Helps determine therapeutic concentrations
  - Allows adjustments for variable drug absorptions
- Documents adherence to treatment
- May reduce toxicities

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Serum Drug Level Monitoring

- Aminoglycosides
  - To reduce toxicity, achieve therapeutic levels
  - In-house (Amikacin) *vs.* send-out (Kanamycin)
- Ethambutol
  - May be useful in renal insufficiency to reduce toxicity
- Rifampin
  - To determine malabsorption (*e.g.,* In severe HIV)
- Cycloserine
  - To determine therapeutic levels

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Discharge Planning

- Start when TB diagnosed or suspected:
  - Clinical/laboratory evidence or patient on TB drugs
- Pre-discharge conference:
  - Include nurse case manager, providers, discharge planners
- Home assessment by nurse case manager necessary to:
  - Prevent putting potentially vulnerable household members at-risk - especially children
  - Coordinate community follow-up for continuation and completion of therapy

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Case management

Activity	Baseline	Month of Treatment Completed 1	2	3	4	5	6	7	8	End of Treatment Visit
MICROBIOLOGY										
Sputum smears and culture[1]	☐	☐	☐	☐	☐					☐
Drug susceptibility testing[2]	☐			☐						
IMAGING										
Chest radiograph or other imaging[3]	☐		☐							☐
CLINICAL ASSESSMENT										
Weight[4]	☐	☐	☐	☐	☐	☐	☐	☐	☐	
Symptom and adherence review[5]	☐	☐	☐	☐	☐	☐	☐	☐	☐	
Vision assessment[6]	☐	☐	☐	☐	☐	☐	☐	☐	☐	
LABORATORY TESTING										
AST, ALT, bilirubin, alkaline phosphate[7]	☐	☐	☐	☐	☐	☐	☐	☐	☐	
Platelet count[8]	☐	☐	☐	☐	☐	☐	☐	☐	☐	
Creatinine[8]	☐	☐	☐	☐	☐	☐	☐	☐	☐	
HIV[9]	☐									
Hepatitis B and C screen[10]	☐									
Diabetes Screen[11]	☐									

ATS/CDC/IDSA Clinical Practice guidelines for TB CID, 2016

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Completion of Therapy

- Completion of treatment primarily defined by number of ingested doses within specified time frame (not solely on duration of therapy)
- For example:
  1. 6-month daily regimen (7 days/wk) = at least 182 doses of INH and RIF, and 56 doses of PZA
  2. 6-month daily regimen (5 days/wk) = at least 130 doses

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Completion of Therapy

- In cases of drug toxicity or non-adherence to regimen, all specified number of doses must be administered within:
  - 3 months for initial phase
  - 6 months for 4-month continuation phase
- If the specified number of doses is not administered within the targeted time period, patient is considered to have interrupted therapy

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Therapy Deviations

- Treatment interruptions: Significance varies with
  - Bacillary load at time of interruption
  - Time in course when interruption occurred (initial or continuation phase)
  - Duration and intermittency of interruption
- Split dosing of first line agents
  - Lowers peak serum concentrations – may encourage emergence of resistance

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Treatment Interruptions in Initial Phase

- If patient has received ≥80% of total doses:
  - Consider bacillary load at time of interruption to decide if additional treatment needed (smear + or smear - ?)
- If patient has received <80% of total doses:
  - Consider duration of lapse and ability to complete full four months of Rx within 6 months time

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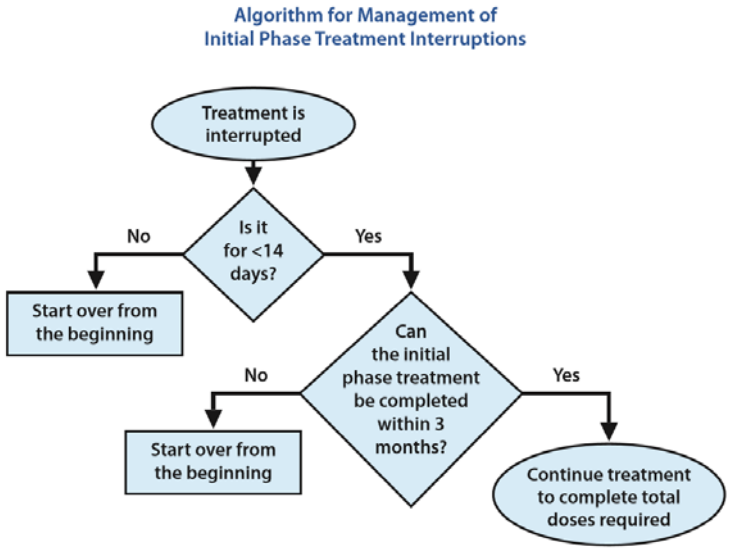

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Treatment Interruptions in Continuation Phase

- If patient received ≥80% of doses and
  - Sputum smear was negative on initial testing, further therapy may not be needed
  - Sputum smear was positive on initial test, continue therapy
- If patient received <80% of doses, and lapse is
  - <3 months long, continue therapy
  - >3 months long, restart therapy from beginning of initial phase

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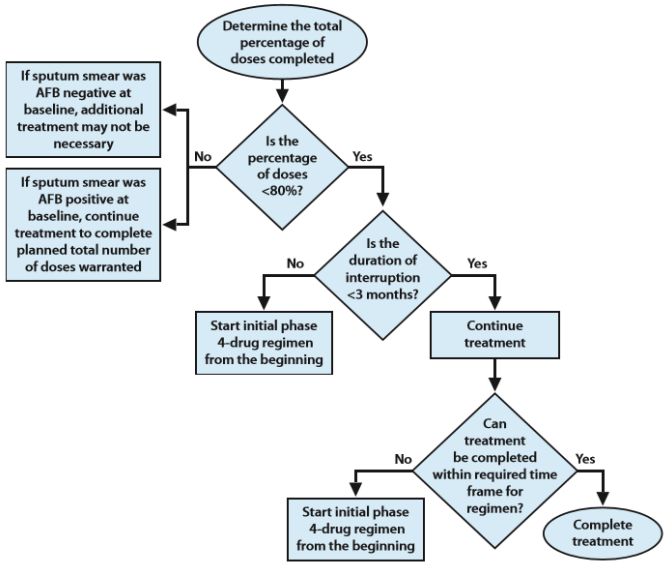
Algorithm for Management of
Continuation Phase Treatment Interruptions



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Special Treatment Situations

- Pregnancy & breastfeeding
- Renal disease
- Indiscrete use of Fluoroquinolones

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TB in Pregnancy

- Treatment for TB is ok
  - HRE + B_6 usual (PZA not used in US) → 9 mos
  - Avoid aminoglycosides (SM, KM, AK), Capreomycin
    - May be assoc w/ fetal deafness
- Consider possible trans-placental spread to infant
  - Prepare for examination of placenta post-delivery for pathology, AFB stains/cultures
  - Alert pediatrician to observe infant for signs of congenital TB
- Separation of mom from infant?

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TB After Pregnancy

- Pediatrician evaluates baby, considers treatment (individualized) for potential trans-placental contact if mother not on Rx prenatally: Review placenta data later
- Baby gets “window treatment plus” (6 months) if non-protected exposure to a case took place after delivery

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Breastfeeding

- Breastfeeding ok – caution among women on fluoroquinolone
- INH given to mother is not adequate as preventive therapy in breastfeeding infant
  - Infant receives drug, may exhibit side effects
  - TB-exposed infant needs own INH, Vit B_6

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Renal Disease

- Increase dosing interval of renally excreted anti-TB drugs (rather than lower dose) if Creatinine clearance decreased (<30ml/min)
  - EMB, PZA, Lqn, aminoglycosides, Capreo, CS
- Consult experts for dosing of patients on dialysis
  - No adjustment for INH & RIF
  - Lengthen interval for EMB & PZA (generally 3x/wk, following dialysis)

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Table 12

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Treatment in Other Special Situations

- Recommendation 7: TB Pericarditis
  - Adjunctive steroids not routinely recommended
    - Conditional recommendation; very low certainty
- Recommendation 8: TB Meningitis
  - Adjunctive steroids for 6-8 weeks
    - Strong recommendation; moderate certainty
  - Use of Ethambutol as 4th drug
- Recommendation 9: Culture negative TB
  - Four months adequate
    - Conditional recommendation; very low certainty

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IDSA / ATS: Empirical Antibiotics for Community Acquired Pneumonia

- Outpatient
  - 1. Previously healthy and no use of antimicrobials within the previous 3 months
    - A macrolide (strong recommendation; level I evidence)
    - Doxycycline (weak recommendation; level III evidence)
  - 2. Presence of comorbidities such as chronic heart, lung, liver or renal disease; diabetes mellitus; alcoholism; malignancies; asplenia; immunosuppressing conditions or use of immunosuppressing drugs; or use of antimicrobials within the previous 3 months (in which case an alternative from a different class should be selected)
    - A respiratory fluoroquinolone (moxifloxacin, gemifloxacin, or levofloxacin [750 mg]) (strong recommendation; level I evidence)
    - A b-lactam **plus** a macrolide (strong recommendation; level I evidence)
- Inpatients, non-ICU
  - A respiratory fluoroquinolone (strong recommendation; level I evidence)
- Inpatients, ICU
  - b-lactam + azithromycin or respiratory fluoroquinolone

From *Table 7:* CID. 44 (suppl. 2), 2007

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Summary

- Person-centered case management is standard of care
- When prescribing treatment
  - Use preferred regimens
  - Extend treatment for cavitation and/or + sputum cultures at 2 months
  - Calculate # doses within prescribed time frame
  - Use DOT as a tool to ensure treatment adherence
- Special situations
  - Be mindful of additional guidelines for pregnant or breastfeeding women, HIV (+) persons, patients with renal or liver disease

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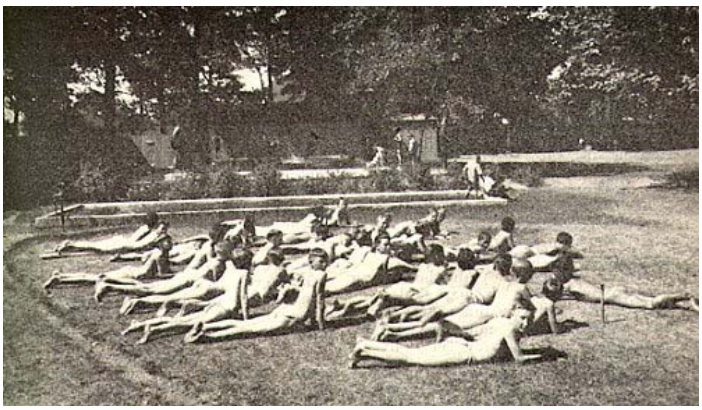

Heliotherapy (sun therapy)
***Valley Echo*, April, 1927**

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