RUTGERS
Global Tuberculosis Institute
NEW JERSEY MEDICAL SCHOOL

Treatment of Tuberculosis

Alfred Lardizabal, MD

Outline

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

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

Payam Nahid,[1] Susan E. Dorman,[2] Narges Alipanah,[1] Pennan M. Barry,[3] Jan L. Brozek,[4] Adithya Cattamanchi,[1] Lelia H. Chaisson,[1] Richard E. Chaisson,[2] Charles L. Daley,[5] Malgosia Grzemska,[6] Julie M. Higashi,[7] Christine S. Ho,[8] Philip C. Hopewell,[1] Salmaan A. Keshavjee,[9] Christian Lienhardt,[6] Richard Menzies,[10] Cynthia Merrifield,[1] Masahiro Narita,[12] Rick O'Brien,[13] Charles A. Peloquin,[14] Ann Raftery,[1] Jussi Saukkonen,[15] H. Simon Schaaf,[16] Giovanni Sotgiu,[17] Jeffrey R. Starke,[18] Giovanni Battista Migliori,[11] and Andrew Vernon[8]

[1]University of California, San Francisco; [2]Johns Hopkins University, Baltimore, Maryland; [3]California Department of Public Health, Richmond; [4]McMaster University, Hamilton, Ontario, Canada; [5]National Jewish Health, Denver, Colorado; [6]World Health Organization, Geneva, Switzerland; [7]Tuberculosis Control Section, San Francisco Department of Public Health, California; [8]Division of Tuberculosis Elimination, National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention, Centers for Disease Control and Prevention, Atlanta, Georgia; [9]Harvard Medical School, Boston, Massachusetts; [10]McGill University, Montreal, Quebec, Canada; [11]WHO Collaborating Centre for TB and Lung Diseases, Fondazione S. Maugeri Care and Research Institute, Tradate, Italy; [12]Tuberculosis Control Program, Seattle and King County Public Health, and University of Washington, Seattle; [13]Ethics Advisory Group, International Union Against TB and Lung Disease, Paris, France; [14]University of Florida, Gainesville; [15]Boston University, Massachusetts; [16]Department of Paediatrics and Child Health, Stellenbosch University, Cape Town, South Africa; [17]University of Sassari, Italy; and [18]Baylor College of Medicine, Houston, Texas

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

Treatment of TB: Objectives

- The treatment of TB is centered on curing the individual patient and decreasing the transmission of TB bacteria to other people
- 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

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

"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

Key Considerations

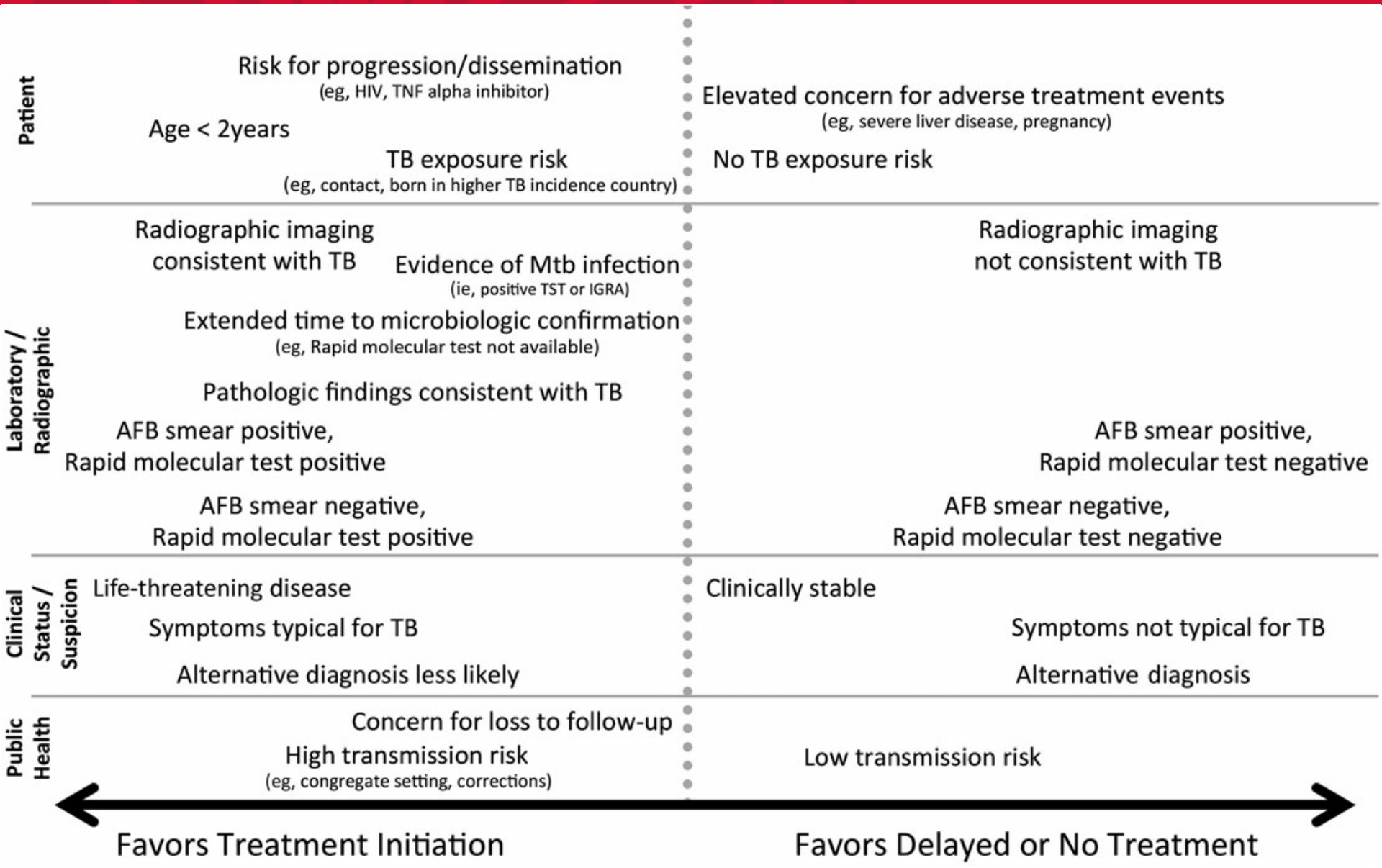
- Recommendation 1: Patient-centered approach
  - Endorses the use of case management
    - Conditional recommendation; very low certainty of evidence
- Recommendation 2: DOT for all forms of TB disease
  - Conditional recommendation; very low certainty in the evidence

CDC 2016

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

Factors to Consider in Empiric Treatment



Clin Infect Dis, 2016:63 (1 October) • e147

Anti-Tuberculosis Drugs in Current Use

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

***Not approved by FDA for use in tuberculosis**

Treatment of Culture-positive Pulmonary Tuberculosis

General Conclusions from the Literature

- 6 months (26 weeks) 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

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

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
  - Sterilizing

Why Do We Use These Drugs?

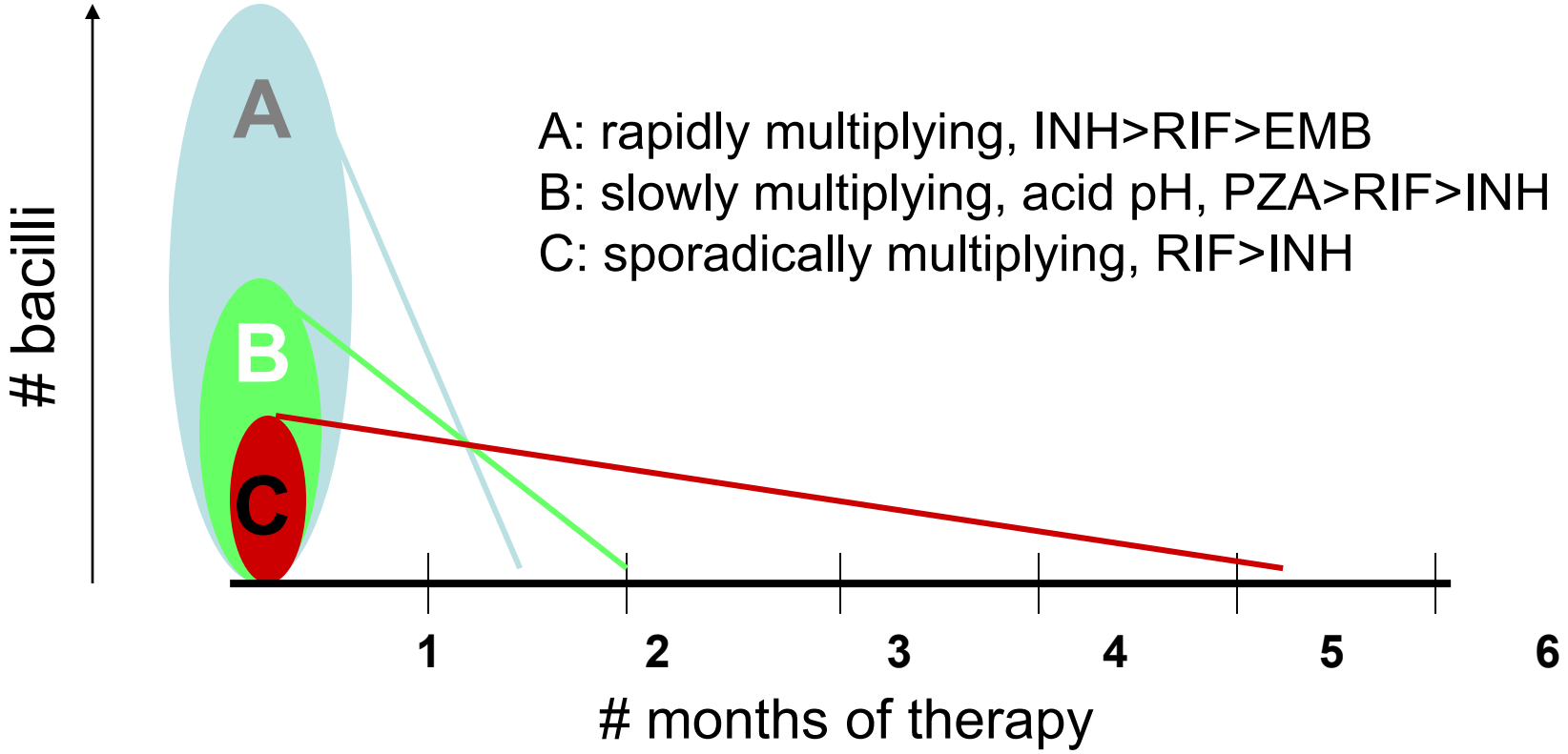
- Each drug has a special role in TB therapy
  - Isoniazid (H, INH): Early bactericidal activity (kill the dividing bacteria)
  - Rifampin (R, Rif): Sterilizing activity (prevents relapse)
  - Pyrazinamide (Z, PZA): Special ‘shortening’ activity
  - Ethambutol (E, EMB): Fortify the regimen to prevent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

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)

Hypothetical Model of TB Chemotherapy

3 anatomic/metabolic populations of bacilli in cavitary TB



M. Iseman, D. Mitchison

Bactericidal

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

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

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

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
- 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?

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

CDC 2016

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 Dose	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.

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")

CDC 2016

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 silicotuberculosis from 20% to 3%

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

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

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

Monitoring for Drug Toxicity

- At baseline
  - ALT, bilirubin, alkaline phos., serum creatinine, and platelet count
  - Eye examination (visual acuity, 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

CDC 2016

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)

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

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

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

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

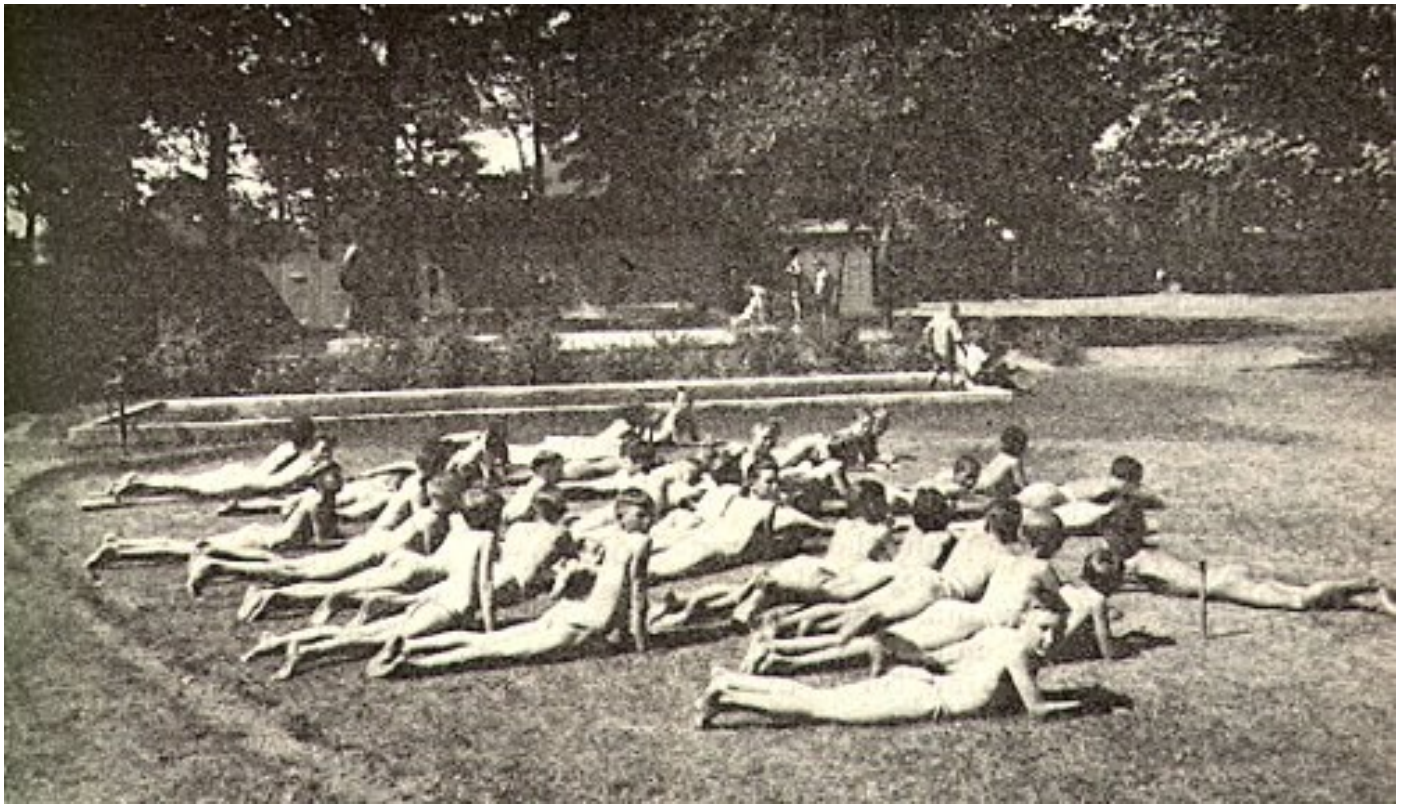
Therapy Deviations

- 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

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



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