TREATMENT OF TUBERCULOSIS INFECTION

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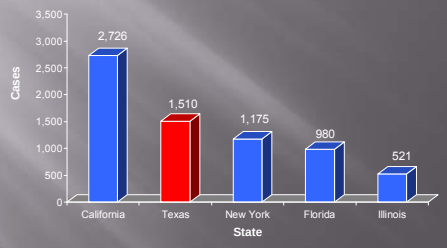
- Goals
  - Review Standard Treatment Regimens
  - Alternative regimens and special cases
  - Monitoring treatment
  - High-risk groups.

- What is Tb?
  - Tb is an infections with an Acid Fast Organism
    - Mycobacterium tuberculosis
    - Usually introduced into the body by inhalation
  - Types of Tb infection
    - Latent
    - Active Tb disease

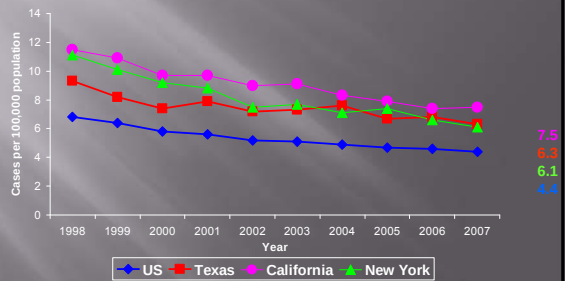
Why is this Important?

Five Leading U.S. States by Number of TB Cases, 2007

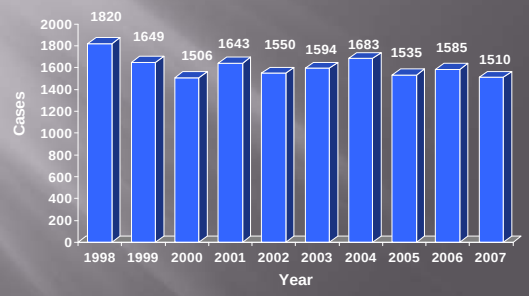


A total of 13,293 TB cases were reported in the U.S. during 2007.
These 5 states represent 52% of the cases reported.
(CA, TX, NY represent 40.7% of the cases.)

Tuberculosis Incidence Rates, Texas and U.S.,1998-2007



Number of TB Cases Texas 1998-2007



There was a 4.7%% decrease in the number of cases from 2006 to 2007.

Top 10 Counties for Cases, 2007

- Harris 397
- Dallas 219
- Tarrant 106
- Hidalgo 76
- Cameron 74
- Bexar 72
- Travis 55
- El Paso 40
- Webb 40
- Fort Bend 40

Total 1119 (74.1%)

Percent of TB Cases With Selected Risk Factors, Texas 2007

Risk Factor	Dallas	Harris	Border	State
Foreign Born	39.7%	49.1%	67.6%	51.4%
Low Income	3.0 %	61.0%	87.0%	45.0%
Alcohol Abuse	16.0%	16.4%	25.0%	12.2%
HIV/AIDS	18.7%	12.1%	5.5%	7.5%
Diabetes	16.0%	14.0%	26.0%	17.0%
Prison/Jail Inmate	4.1%	6.8%	16.7%	8.8%
Noninjecting Drug Abuse	1.4%	5.3%	12.1%	6.2%
Homeless	9.6%	4.3%	1.2%	4.2%
Health Care Worker	2.3%	2.8%	2.0%	2.6%
Injecting Drug Abuse	1.8%	1.8%	5.8%	2.6%
Migrant Farm Worker	0.0%	0.3%	2.0%	0.5%

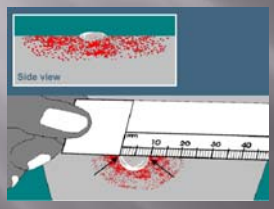
*Note: Individuals can have more than one risk factor.

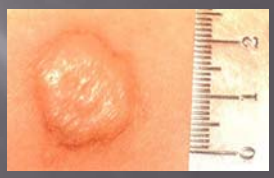
- Diagnosis of Tb
  - Medical History
    - Exposure to persons with disease
    - Cough . 3 weeks
    - Hemoptysis
    - Weakness/fatigue
    - Weight loss
    - Decrease appetite
    - Fever/chills
    - Night sweats

- Diagnosis of Tb
  - Medical History
- Family History
  - Relatives/friends with disease
- Social History
  - Travel history
    - Lived out side US
    - Travel to countries with Tb

- Physical Exam
  - General
    - Cachexia
  - Lungs
    - Rales/rhonchi/crackles

Tb Skin Testing





PPD results and Medical disorders

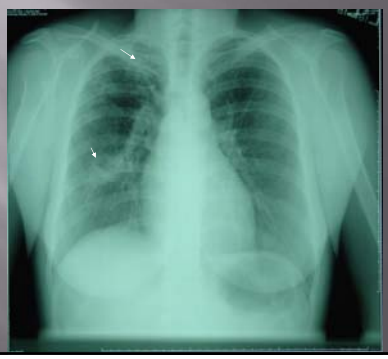
- 5 mm - High Risk Patients
  - HIV(+) patient
  - Abnormal x-ray (“old” Tb)
  - Chronic immunosuppression
- 10 mm - Recent Immigrants Countries with Tb
  Chronic disease (DM, ESRD, Silicosis)
- 15 mm - No medical disorder which alters cell mediated defenses

Tb Skin Testing Significance

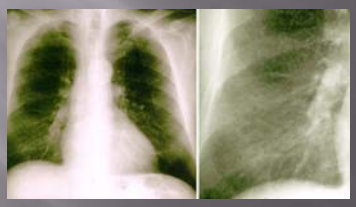
A positive PPD implies risk for developing active disease

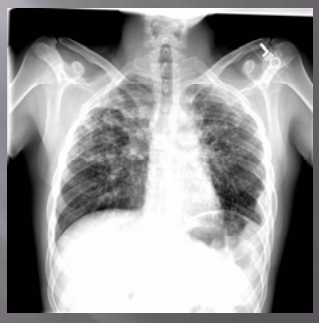
- within 2 years of infection ≈ 5%
- after 2 years but within lifetime ≈5%

TB in a Recent Refugee

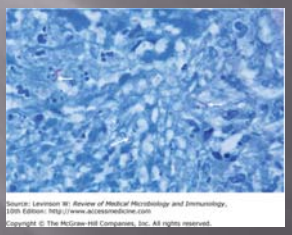


Chest X-Ray





Acid Fast Bacillus



Increasing Complexity of TB Control Efforts

- Foreign born
- Drug Resistant
- TB in recipients of TNF alpha blockers
- TB in transplants
- TB in dialysis and chronic renal failure
- HIV TB
- MDR TB
- Decreasing clinical experience
- Loss of traditional experienced workers
- TB care is more specialized
- Shift of services to private sector
  - Providers may see only one case in a lifetime of practice

- Therapy of Tb follows several basic principles
  - Successful therapy requires more than one drug
  - Drugs must be given in appropriate doses
  - Drugs must be taken regularly
  - Therapy must be continued for an appropriate time

Antituberculosis Drugs

First-Line Drugs	Second-Line Drugs
• Isoniazid	• Streptomycin
• Rifampin	• Cycloserine
• Pyrazinamide	• p-Aminosalicylic acid
• Ethambutol	• Ethionamide
• Rifabutin*	• Amikacin or kanamycin*
• Rifapentine	• Capreomycin
	• Levofloxacin*
	• Moxifloxacin*
	• Gatifloxacin*

* Not approved by the U.S. Food and Drug Administration for use in the treatment of TB

CDC

First Line Anti Tb Drugs

- Isoniazid —
  - is bactericidal;
  - easily tolerated orally in a single daily dose
  - inexpensive
  - major toxicity is hepatitis, which is age-dependent
  - Peripheral neuropathy is uncommon, and can be minimized by using pyridoxine.
  - Pyridoxine supplementation (25 to 50 mg per day in adults)

First Line Anti Tb Drugs

- Rifampin —
  - is bactericidal for M. tuberculosis
  - single daily oral dose: well tolerated. Hepatic toxicity is less common than with INH
  - rifampin induces hepatic microsomal enzymes and may increase hepatic clearance and decrease the effectiveness of a number of drugs
  - Rifampin is excreted as a red-orange compound in urine, tears, sweat, and stool, and may discolor these fluids and permanently stain contact lenses.

First Line Anti Tb Drugs

- Pyrazinamide —
- is bactericidal for M. tuberculosis at an acid pH (e.g., inside cells).
- is effective orally as a single daily dose,
- gastrointestinal intolerance is common.
- The major toxicity is hepatic injury, similar to that seen with INH and RIF.
- Treatment of latent tuberculosis infection with a two month course of RIF/PZA is associated with severe hepatic toxicity and is not recommended.

First Line Anti Tb Drugs

- Ethambutol —bacteriostatic
- Single daily oral dose
- The major toxicity is optic neuritis, which is uncommon at a dose of 15 mg/kg
- At higher doses; red-green color blindness may develop

Tb Therapy

- Latent Tb
  - Preferred: INH 300 mg po qd x 9 months
  - Alternate regimens
    - INH 300 mg po qd x 6 months
    - INH 900 mg po twice weekly x 9 months
    - INH 900 mg po twice weekly x 6 months
    - Rifampin 600 mg po qd x 4 months

Active Tb

- Four potential regimens for treating Tb
  - Each regimen as an initial phase, consisting of multiple drugs for a period of time, approximately 2 months
    - Regimen 1 and 4; daily for two months
    - Regimen 2; daily for two weeks, then twice weekly for 6 weeks
    - Regimen 3; Three times weeks for 8 weeks

Therapy for Active Tb

- Continuation phase
  - Given for 4 to 7 months of therapy
  - In most cases consist of INH and RIF
- Candidates for 9 months of therapy
  - Cavitary pulmonary Tb
  - Patients not receiving PZA in initial phase
  - Sputum culture remaining positive after 2 months of therapy

Tb therapy Regimens

Drug regimens for culture-positive tuberculosis caused by drug-susceptible organisms

Initial phase			Continuation phase			Range of total doses minimal duration	Rating*	
Regimen	Drugs	Interval and doses †, minimal duration	Regimen	Drugs	Interval and doses †‡, minimal duration		HIV-	HIV+
1	INH RIF PZA EMB	Seven days per week for 56 doses (8 wk) or 5 d/wk for 40 doses (8 wk)Δ	1a	INH/RIF	Seven days per week for 126 doses (18 wk) or 5 d/wk for 90 doses (18 wk)Δ	182-130 (26 wk)	A	A
			1b	INH/RIF	Twice weekly for 36 doses (18 wk)	92-76 (26 wk)	A	A§
			1c¥	INH/RPT	Once weekly for 18 doses (18 wk)	74-58 (26 wk)	B	E
2	INH RIF PZA EMB	Seven days per week for 14 doses (2 wk), then twice weekly for 12 doses (6 wk) or 5 d/wk for 10 doses (2 wk)Δ, then twice weekly for 12 doses (6 wk)	2a	INH/RIF	Twice weekly for 36 doses (18 wk)	62-58 (26 wk)	A	B§
			2b¥	INH/RPT	Once weekly for 18 doses (18 wk)	44-40	B	E
3	INH RIF PZA EMB	Three times weekly for 24 doses (8 wk)	3a	INH/RIF	Three times weekly for 54 doses (18 wk)	78 (26 wk)	B	B
4	INH RIF EMB	Seven days per week for 56 doses (8 wk)Δ or 5 d/wk for 40 doses (8 wk)	4a	INH/RIF	Seven days per week for 217 doses (31 wk) or 5 d/wk for 155 doses (31 wk)Δ	273-195 (39 wk)	C	C
			4b	INH/RIF	Twice weekly for 62 doses (31 wk)	118-102 (39 wk)	C	C

EMB: ethambutol; INH: isoniazid; PZA: pyrazinamide; RIF: rifampin; RPT: rifapentine.
* Definitions of ratings: A: preferred; B: acceptable alternative; C: offer when A and B cannot be given; E: should never be given.
† When DOT is used, drugs may be given 5 days/week and the necessary number of doses adjusted accordingly. Although there are no studies that compare five with seven daily doses, extensive experience indicated this would be an effective practice.
‡ Patients with cavitation on initial chest radiograph and positive cultures at completion of 2 months of therapy should receive a 7-month (31-week; either 217 doses [daily] or 62 doses [twice weekly]) continuation phase.
Δ Five-day-a-week administration is always given by DOT. Rating for 5 day/week regimens is A.
§ Not recommended for HIV-infected patients with CD4+ cell counts < 100 cells/ml.
¥ Options 1c and 2b should be used only in HIV-negative patients who have negative sputum smears at the time of completion of 2 months of therapy and who do not have cavitation on the initial chest radiograph (see text). For patients started on this regimen and found to have a positive culture from the two month specimen, treatment should be extended an extra three months.
Data from Am J Respir Crit Care Med 2003; 167:603.

Treatment of Culture-Positive TB (1)

(Rated: AI in HIV-negative, AII in HIV-positive patients)

Initial Phase

2 months - INH, RIF, PZA, EMB daily (56 doses, within 8 weeks)

Continuation Phase

Options:

1) 4 months - INH, RIF daily (126 doses, within 18 weeks)
2) 4 months - INH, RIF twice / week (36 doses, within 18 weeks)
3) 7 months - INH, RIF daily (217 doses, within 31 weeks)*
4) 7 months - INH, RIF twice / week (62 doses, within 31 weeks)*

* Continuation phase increased to 7 months if initial chest x-ray shows cavitation and specimen collected at end of initial phase (2 months) is culture positive

CDC

Treatment of Culture-Positive TB (2)

Twice-Weekly Options

(Rated: AII for HIV-negative, BII for HIV-positive patients*)

Initial Phase

0.5 months - INH, RIF, PZA, EMB daily (10-14 doses, within 2 weeks)
THEN
1.5 months - INH, RIF, PZA, EMB twice / week (12 doses, within 6 weeks)

Continuation Phase

Options:

1) 4 months - INH, RIF twice / week (36 doses, within 18 weeks)
2) 7 months - INH, RIF twice / week (62 doses, within 31 weeks)

* Regimen rated BII for HIV-positive patients with CD4+ T-lymphocytes cell count >100/µl. Not recommended for those with CD4+ T-lymphocytes cell count < 100/µl

CDC

Treatment of Culture-Positive TB (3)

Thrice-Weekly Options

(Rated: BI for HIV-negative, BII for HIV-positive patients)

Initial Phase

2 months - INH, RIF, PZA, EMB 3 times / week (24 doses, within 8 weeks)

Continuation Phase

Options:

1) 4 months - INH, RIF 3 times / week (54 doses, within 18 weeks)
2) 7 months - INH, RIF 3 times / week (93 doses, within 31 weeks)

CDC

Treatment of Culture-Positive TB (4)

Regimens without Pyrazinamide

(Rated: CI for HIV-negative, CII for HIV-positive patients)

Initial Phase

2 months - INH, RIF, EMB daily (56 doses, within 8 weeks)

Continuation Phase

Options:

1) 7 months - INH, RIF daily (217 doses, within 31 weeks)
2) 7 months - INH, RIF twice / week (62 doses, within 31 weeks)*

* Twice weekly dosing is not recommended for persons with CD4+ T-lymphocytes cell count < 100/µl

CDC

Tb Therapy

- Advantages of Directly Observed Therapy
  - Lower rate of primary drug resistance:
    - 6.7% vs. 13 %
  - Lower rate of acquired drug resistance
    - 2.1% vs. 14%
  - Lower relapse rate
    - 5.5% vs. 20.9%
  - Lower relapse rate with resistant AFB
    - 0.9% vs. 6.2%

Management in Special Circumstances

- Rifampin Intolerance
  - 9 to 12 months of INH, PZA, and EMB
- HIV
  - Tb tends to progress rapidly in HIV patients
  - HIV patients should be treated early
  - Smear positive Tb patients should be isolated for HIV

Special Circumstances: HIV

- Drug Interactions with Rifampin
  - HAART (Protease inhibitors and efavirenz)
  - Medications for other co morbidities
    - Itraconazole, Fluconazole
    - Clarithromycin
    - Methadone
    - Coumadin
    - Immunosuppressive therapy for transplants
    - Chemotherapeutic agents

Rifabutin may be a good substitute to minimize interactions

Management in Special Circumstances

- Diabetes
  - Incidence of Tb in diabetic patients is 2 to 4 fold higher in diabetic patients than in the non-diabetic
  - After 6 months of therapy, odds of remaining culture positive are 7 fold higher in the diabetic
  - Effects of tighter glucose control are not known

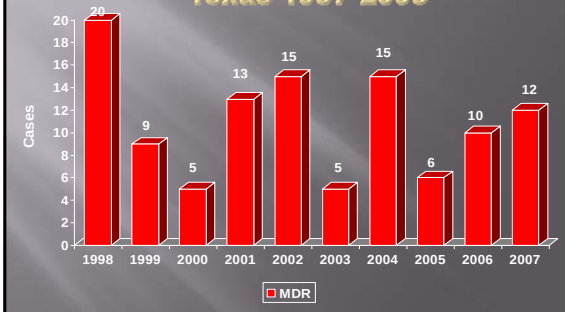
Management in Special Circumstances

Multidrug resistant Tb

World wide this is an increasing problem

Initial standard therapy is modified by adding additional drugs to insure at least 4 drugs are effective.

Number of MDRTB Cases Texas 1997-2006



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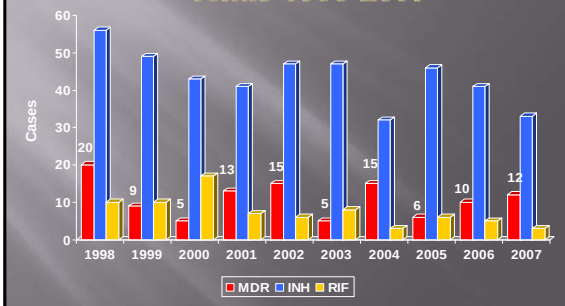


What is Multi Drug-Resistant (MDR) TB?

- Resistant to both INH and RIF
- More difficult to treat
  - More drugs are required to treat patient
  - Often less effective at killing the bacilli
  - Often cause more adverse reactions
- Treatment longer; 2 years or more

Extra pulmonary TB

- Treatment regimens similar to pulmonary TB EXCEPT for
  - -TB meningitis – optimal therapy still not defined; 9-12 months recommended (AIII)
  - Disseminated TB in children
  - ?? Disseminated TB in adults
    - Can you really use 6 month therapy?

Active TB During Pregnancy

- Treatment:
  - INH, Rifampin, Ethambutol x 9 months
    - Stop ethambutol if susceptible to INH and rifampin
- Follow carefully for hepatotoxicity
  - During pregnancy
  - Three months postpartum

Tb in RA Patient Warnings

- Remicade should not be given in patients with a clinically important active infection.
- Caution…when considering the use of Remicade in patients with a chronic infection or a history of recurrent infections.
- Patients should be monitored for signs and symptoms of infection while on or after treatment with Remicade.
- If a patient develops a serious infection Remicade should be discontinued.

PDR 2004

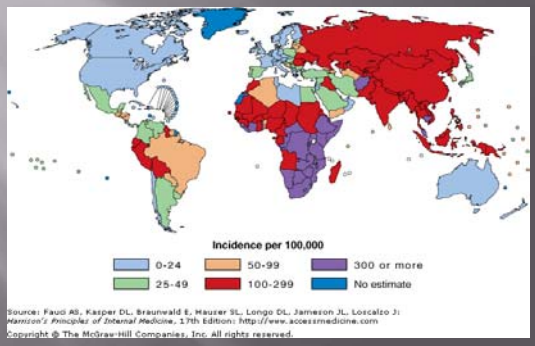
Therapy in Special Situations Renal Disease

- No change in dose or dosing interval for INH and Rifampin even with severe renal disease
- If creatinine clearance <30
  - Modify dosing intervals of EMB and PZA
  - If sensitivity known, treat with I,R, +/- PZA
- Dose medications after dialysis
- Serum drug levels especially for EMB

Monitoring

- Serial Chest X-Rays
  - Radiographic changes lag therapeutic response
  - Serial Chest X-Rays not routinely performed
  - Chest X-Ray after therapy completed may be used for comparison in the future
- Hepatitis is most common adverse effect of Tb therapy
- Patients should be educated to look for
  - Change in appetite
  - Change in color of urine
- Older patients, patients with hepatitis, ETOH consumption may require monthly LFT

Summary



Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine*, 17th Edition: http://www.accessmedicine.com