



Tuberculosis
Diagnosis and Treatment

Richard B. Kohler, MD
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Overview


- Diagnosis
 - Clinical considerations
 - Laboratory considerations
- Treatment
 - Routine
 - Variants

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TB Diagnosis: When to Suspect

- Cough illness $\geq 2-3$ weeks +
 - Fever, night sweats, weight loss, and/or hemoptysis
- High risk for TB, unexplained illness, including respiratory symptoms of $\geq 2-3$ weeks duration
 - Recent exposure, known (+) TST, HIV, drug use, immigrant ≤ 5 years from high-risk region, high-risk congregate setting, homeless, immunosuppressed, advanced CKD, silicosis, others
- HIV (+), unexplained cough, fever
- High risk and unresponsive CAP after 7 days
- High risk and worrisome CXR

Guidelines. MMWR 54:1 (2005)

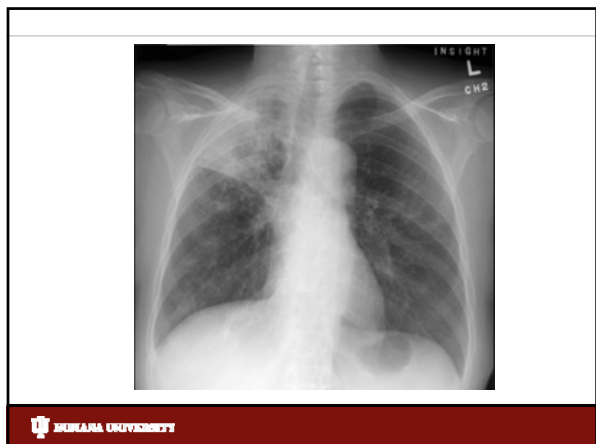
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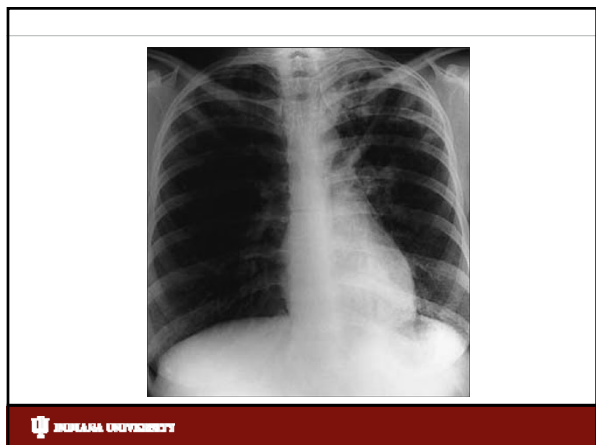
Suggestive Radiologic Findings

- Infiltrates in upper lobes or superior segments of lower lobes












Sputum Analysis in TB


- Recommendations: Submit 3 specimens for AFB smears and cultures
 - Labs report that ~25% of requests for AFB smears and cultures are submitted as the one and only specimen.
- Culture (+)
 - #1: ~75%
 - #1 + #2: ~90%
 - #1 + #2 + #3: ~95%
- Smear (+) About 60% (45-80%) of patients
 - Roughly 40% of patients with culture-proven pulmonary TB never have a positive smear

Nelson et al; J Clin Micro 1998;36:467;
Craft et al J Clin Micro 2000;38:4285



Lab Evaluation: Sputum Analysis


- AFB smear microscopy
 - o Sensitivity 45-80% (culture (+) cases)
 - o Lower in children
- AFB culture
 - o Sensitivity ~80% (most of rest are "smear-negative culture-negative" TB)
 - o Specificity ~98% (false positives due to contaminated equipment, lab cross-contamination)



Rates of False (+) Cultures for Mycobacterium tuberculosis

Study	False (+)/Total	Rate
1	3/114	2.6%
2	9/496	1.8%
3	9/259	3.5%
4	12/441	2.7%
5	4/463	0.9%
6	24/306	7.8%
7	5/173	2.9%
8	3/105	2.9%
9	0/210	0
10	8/199	4.0%
11	46/1439	3.2%

Burman W, Reves R., CID 2000;31:1390



Nucleic Acid Amplification Tests

TB/Total	Smear	Sensitivity	Specificity
1262/2241	+	94.3%	98.1%
75/170	-	70.8%	85.9%

Laraque F et al., CID 2009;49:46-54

Smear	Sensitivity	Specificity
+	95%	98%
-	75-78%	95%

UpToDate 2009

Predictive Value, Positive NAAT, in Smear (-) TB				
Test Parameter		TB Prevalence		
Sensitivity	Specificity	50%	30%	10%
75%	86%	84%	70%	37%
75%	95%	94%	87%	62%

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Lab Evaluation: Nucleic Acid Amplification

- 2009 CDC guidelines recommend routine use when suspicion moderate to high
 - Some kits approved for smear (-) sputum, some not.
 - Can detect 50-80% of AFB smear-negative, culture-positive cases.
 - When clinical suspicion of TB is low, positive predictive value <50%.
- Guideline:
 - Routinely collect, process, and test.
 - At least one specimen, preferably the first, should be [appropriately process] and tested using an NAA test.

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MMWR 2009 (January 16);58:7-10


Treatment of Pulmonary TB

- How long?
- What drugs?
- How?

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TB Treatment: Duration (with Standard Regimen)

- Most pulmonary 6 months
- Lymph node 6 months
- Pleural 6 months
- Pericardial 6 months
- Disseminated 6 months
- GU 6 months
- Peritoneal 6 months



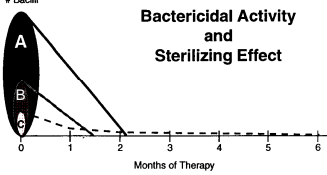
TB Treatment: Duration (with Standard Regimen)

- Special pulmonary situations
 - Sputum culture (+) at 2 months and cavity:
 - 9 months
 - Adult smear (-), culture (-):
 - 4 months
- Bone/joint: 6-9 months
- CNS 9-12 months




Hypothetical Model of TB Chemotherapy

- 3 "Populations" of bacilli in cavitary TB
- Variables of these populations: anatomic, and/or metabolic




Bactericidal Activity and Sterilizing Effect

Pop. A = Rapidly multiplying (caseum)	Drug activities: INH>>SM>>RIF>>EMB
Pop. B = Steadily multiplying (acidic)	Drug activities: PZA>>RIF>>INH
Pop. C = Sporadically multiplying	Drug activities: RIF>>INH



Preferred TB Regimen for Pan-Sensitive Isolates (Standard Regimen)


- First 2 months: RIPE
Rifampin
Isoniazid
Pyrazinamide
Ethambutol (stop if RIP susceptible)
- Final 4 months: RI



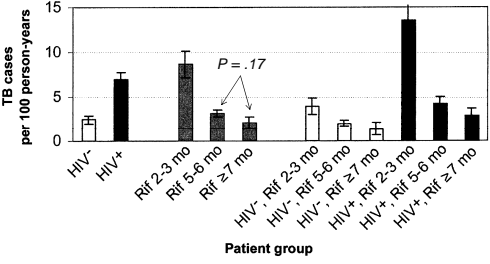
Effectiveness of Standard Regimen

Initiate	Mo.	Continue	Mo.	Relapse (%)	C (-) 2 mo.	n
RIP	2	RI	4	3.4	85	116
RIP	2	RI	4	4.1	--	330
RIP	2	RI	4	2.9	90	140
RIP	2	RI	4	3.5	80	206
RIP	2	RI	4	6.5	--	337
RIPE	2	RI	4	2.5	--	132


Poland, 1984, Am Rev Respir Dis 130:1091; US, 1990, Ann Int Med 112:397; Africa 1988, Am Rev Respir Dis 137:1147; Brazil 1989, Lancet 2:1174



TB Recurrence Rates: Meta-Analysis



Korenromp E et al; Clinical Infect Dis 2003;37:101



TB Relapses in 6-Month Regimen

- Twice weekly RI in continuation phase
- | | |
|------------------------------------|----------|
| Cavity, culture (+) at 2 months | 21% (48) |
| Cavity, culture (-) at 2 months | 5% (150) |
| No cavity, culture (+) at 2 months | 6% (17) |
| No cavity, culture (-) at 2 months | 2% (181) |

Lancet 2002;360:528-534; MMWR 2003;52:35

■ Similar findings also in two prior studies



Extend Treatment to 9 Months

- Combination of cavitory disease and positive culture at 2 months.



Isolated or Combined INH Resistance

- World-wide resistance to INH in 2005 was about 8%.
- Major outliers: Kazakhstan (43%); Tomsk Oblast (Russia); 29%; Latvia (29%); Israel (26%); Lithuania (25%), Liaoning Province (China) 25%; North Arcot (India) 23%; Estonia (23%)
- Indiana: Last 5 years 27/671 (4.0%); 2007 10/129 (7.8%)

WHO: Anti-tuberculosis drug resistance in the world report no. 3 (2004); http://www.who.int/tb/publications/who_htm_tb_2004_343/en/index.html



INH Resistant TB: Can Still Use 6-Month Therapy

- As long as isolates remain susceptible to rifampin and two other drugs, six month regimens are effective.
- With rifampin + 2 or more other active drugs, in 12 studies done in Africa, Hong Kong, and Singapore, success rate for 6-month regimens was over 95%. (n ~ 246 patients)
- In 11 patients, rifampin resistance was present, and 5 failed treatment.

Mitchison, DA, Nunn, AJ. Influence of initial drug resistance on the response to short-course chemotherapy of pulmonary tuberculosis. Am. Rev Respirator Dis 1986;133:423-430.



Moxifloxacin vs INH: 2-Month Results: Culture-Negative Sputa

REGIMEN	S (-)/TOTAL	% S (-)	p
RIPE	90/164	54.9%	0.37
RMPE	99/164	60.4%	

Dorman S et al., AJRCCM 2009;180:273



Rifampin Resistance: 6-Month Course Not Adequate

- Short course (6-month) treatment cannot be used for any rifampin resistant isolate.
- For isolated rifampin resistance, use 12 – 18 months of INH, ethambutol, fluoroquinolone supplemented by pyrazinamide during first two months. INH + PZA + streptomycin for 9 months can work but is difficult for patients to tolerate.
- For INH and rifampin resistance, use 18 – 24 months of pyrazinamide, ethambutol, fluoroquinolone, streptomycin.

ATS/CDC/IDSA Guidelines. MMWR 2003;52:69

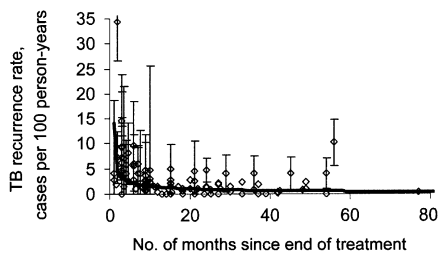


Culture-Negative Smear-Negative Pulmonary Tuberculosis in Adults

- U.S.: ~15% of pulmonary TB is culture (-)
- 4-month RI (rifampin + isoniazid) regimen
→99% success rate (1.2% relapse rate at ~44 months)
(Dutt et al., ARRD 1989;139:867-870)
- ATS/IDSA/CDC guidelines recommend RIPE for first 2 months then RI for 2 months.
- AFB smear (+) culture negative cases (clinically highly suspicious for TB) should be treated with 6-month regimen.



Time to Relapse in TB (HIV (-))



Korenromp et al; Clinical Infect Dis 2003;37:101



TB Risk of Relapse by Dosing Schedule

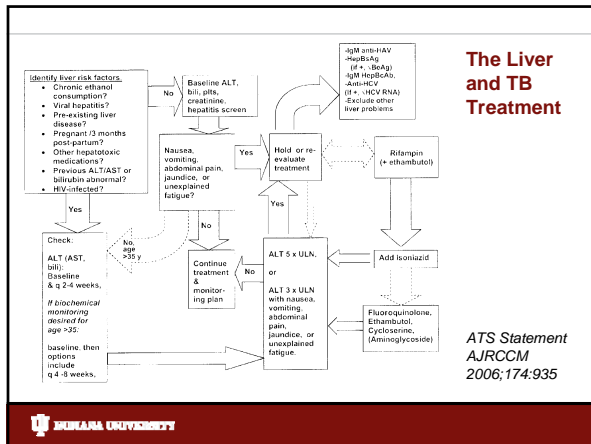
IP	CP	N	Cavity		No Cavity	
			Cit2m+	Cit2m-	Cit2m+	Cit2m-
Daily	Daily	1554	6.0%	2.2%	1.8%	0.6%
Daily	3XW	410	6.1%	3.3%	2.2%	1.2%
Daily	2XW	506	15.6%	5.7%	5.4%	1.9%
3XW	3XW	1853	14.5%	5.3%	4.6%	1.7%
2XW	2XW	108	2.5%	0.9%	0.8%	0.3%

Relative Relapse Risk All Patients

IP	CP	Relative Risk
Daily	Daily	1.0
Daily	3XW	1.6 (0.6-4.1)
Daily	2XW	2.8 (1.3-6.1)
3XW	3XW	2.8 (1.4-5.7)

Chang KC et al.,
AJRCCM 2006;174:1154
(Systematic Review)





- TB Drugs: Pipeline**
- Fluoroquinolones: moxifloxacin (Ph 3)
 - Oxazolidinones: linezolid
 - Diarylquinoline (TMC207) (Tibotec/J&J) (Ph 2)
 - Nitroimidazoles (OPC67683; PA824) (Otsuka; Pathogenesis) (Ph 2; Ph 2)
 - Pyrrole (LL3858) (Lupin) (Ph 1)
 - Diamine (ethambutol-like) (SQ109) (Squibb) (Ph 1)

- Summary**
- Treatment is usually RIPE X 2 months then RI X 4 months
 - Promising new drugs are in the pipeline
