
بسم الله الرحمن الرحيم

Tuberculosis

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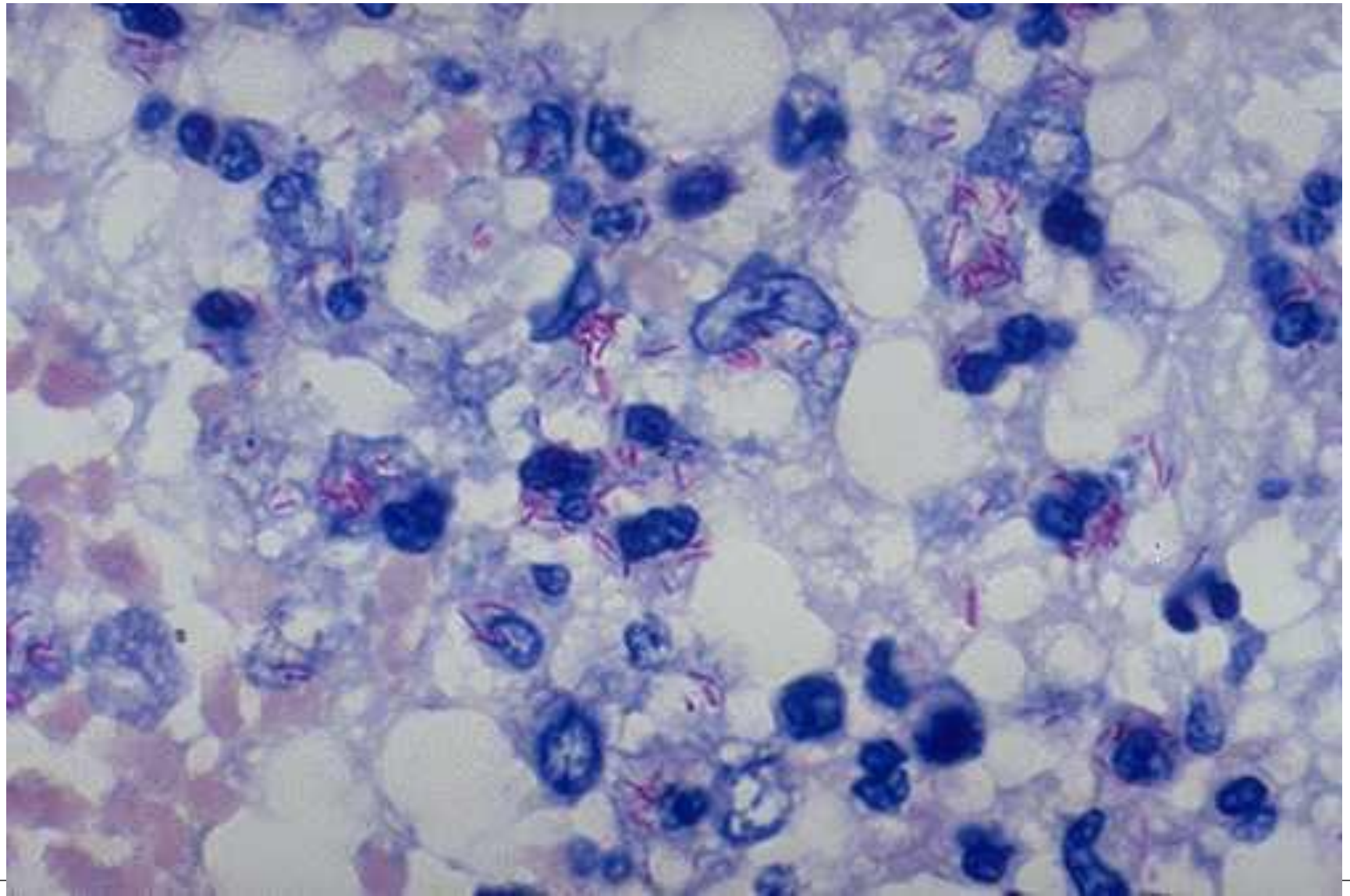
Tehran University of Medical Sciences

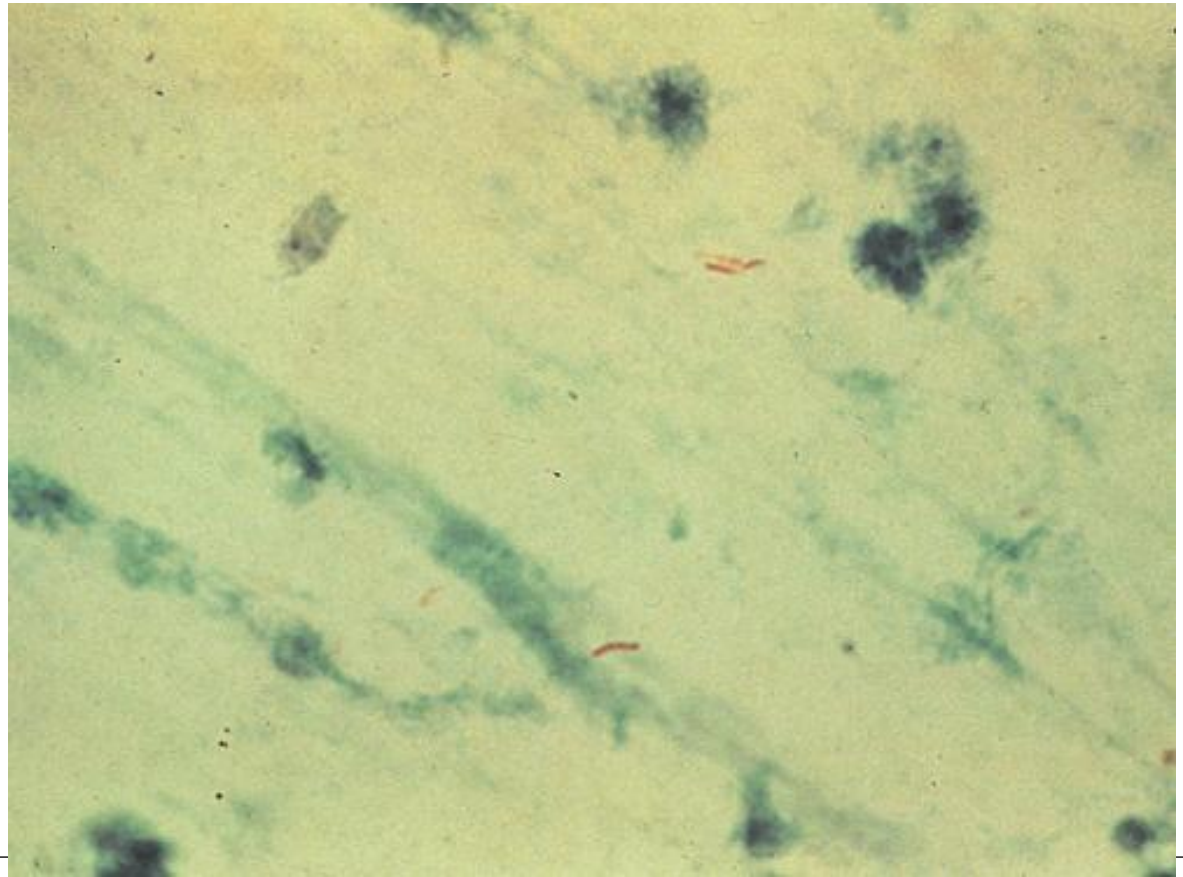
Acid-Fast Staining

AFB - Ziehl-Nielson stain

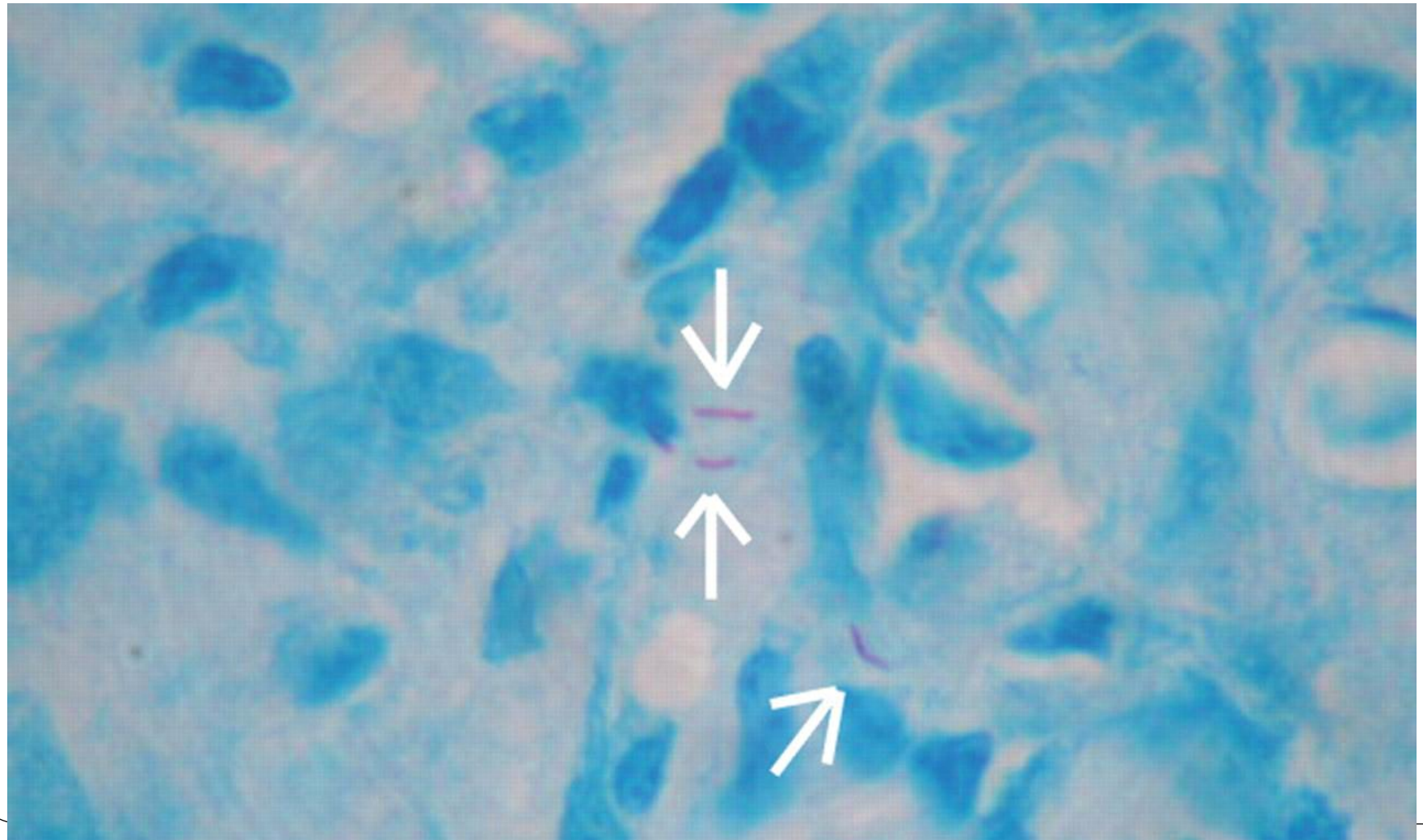


- The organisms appear as slightly bent, beaded rods 2 to 4 μm long and 0.2 to 5 μm wide.

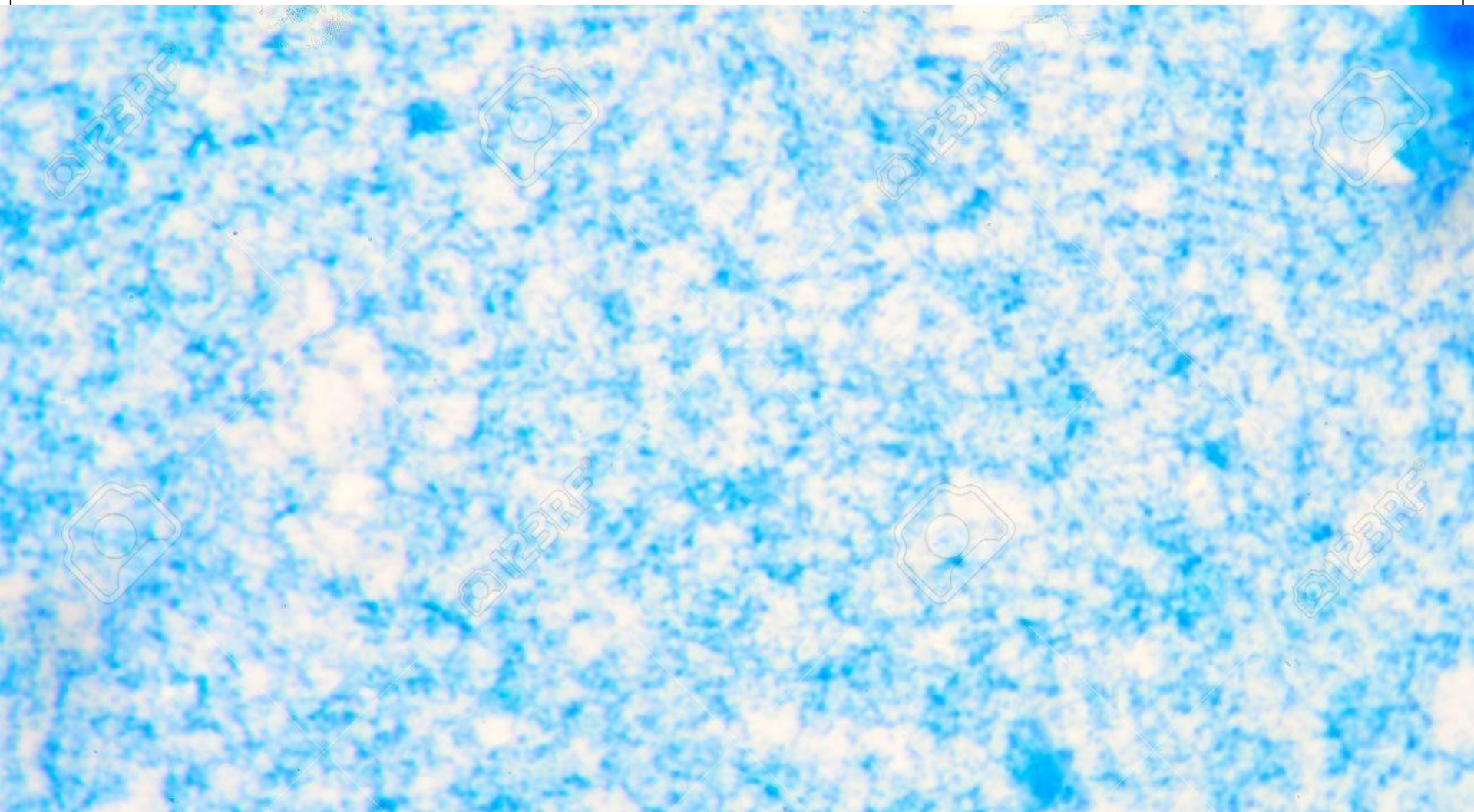
- In sputum they often lie parallel or two organisms adhere at one end to form a V. An estimated 10,000 organisms/mL of sputum are required for smear positivity,



- The sensitivity of sputum acid-fast bacillus smear when compared with culture is approximately 60%.



- Sensitivity is significantly lower with noncavitary disease and HIV infection.



- Sensitivity increases by approximately 10% with the collection of a second sputum sample, and 2% with a third.

- We recommend that acid-fast bacilli (AFB) smear microscopy in all patients suspected of having pulmonary TB
- negative AFB smear result does not exclude pulmonary TB.
- Testing of 3 specimens is considered
- Providers should request a sputum volume of **at least 3 mL**,but the **optimal volume is 5–10 mL**.
- fluorescence microscopy are preferred.

Culture Methods for *M. tuberculosis*

- Culture is the **gold standard** for detecting mycobacteria in clinical specimens.
- Three types of media may be used for culture of mycobacteria:

✓ Solid egg-based (e.g., Lowenstein-Jensen)

✓ solid agar-based (e.g., Middlebrook 7H11)

✓ liquid broth (e.g., Middlebrook 7H12).

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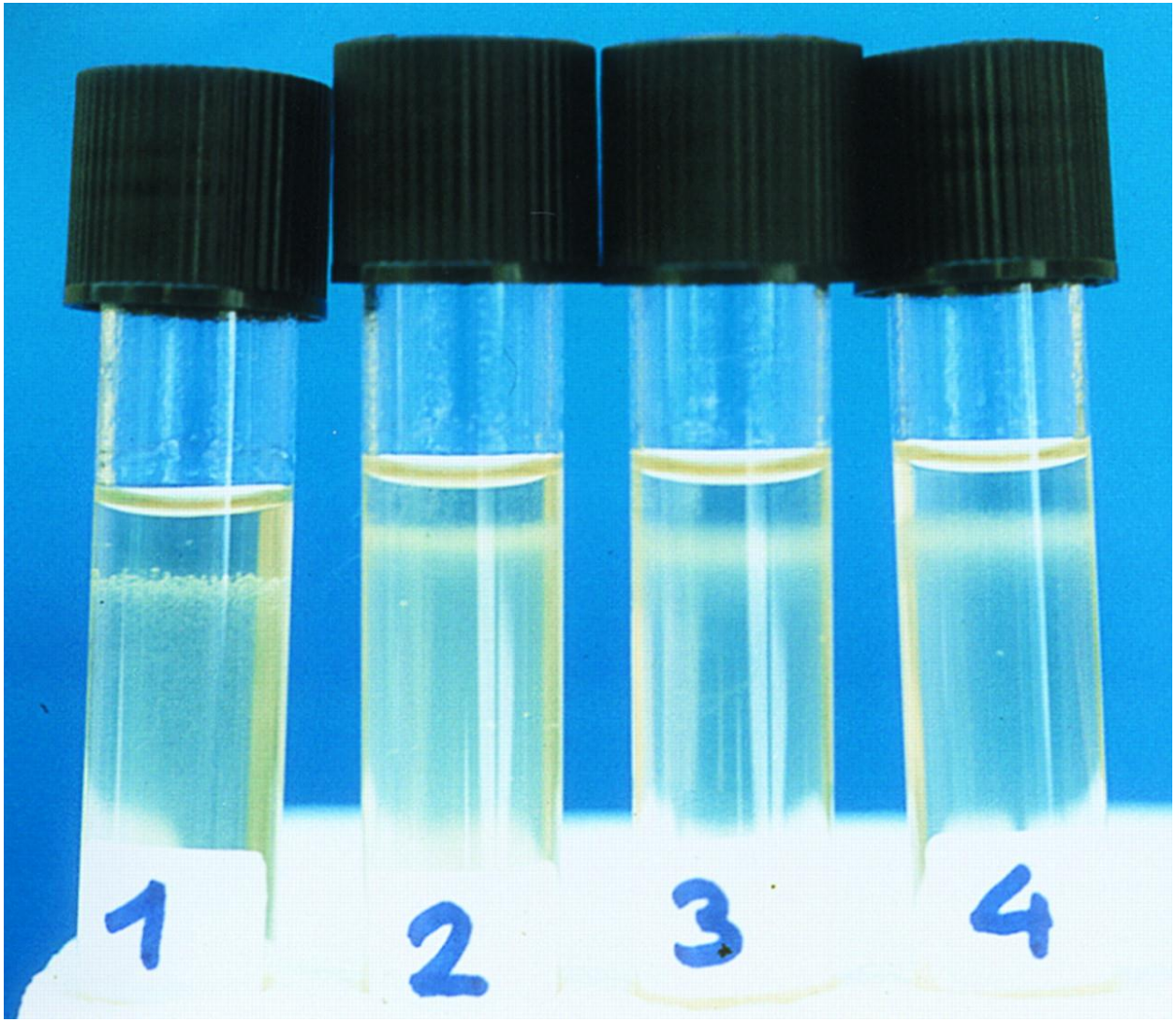
- ✓ liquid broth (e.g., Middlebrook 7H12).



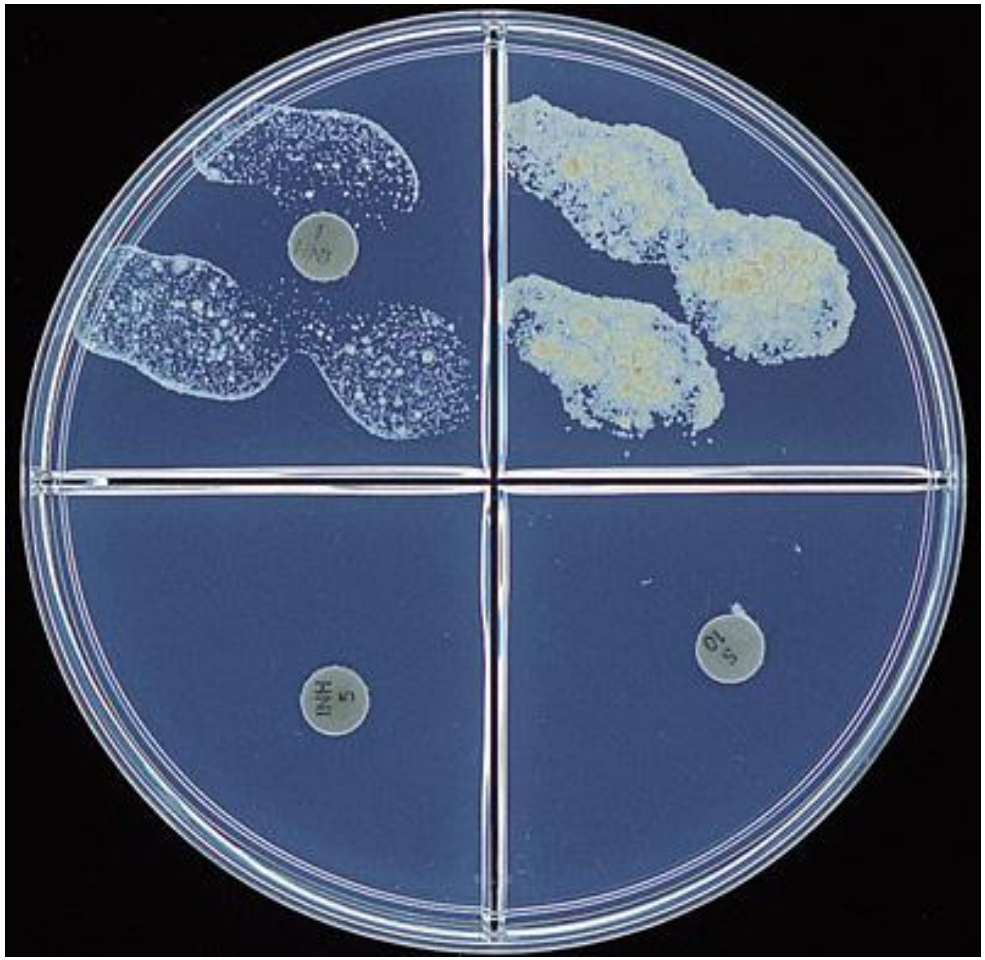
- Media are Liquid broth cultures require 1 to 3 weeks of incubation for detection of organisms

- Solid media, require 3 to 8 weeks.

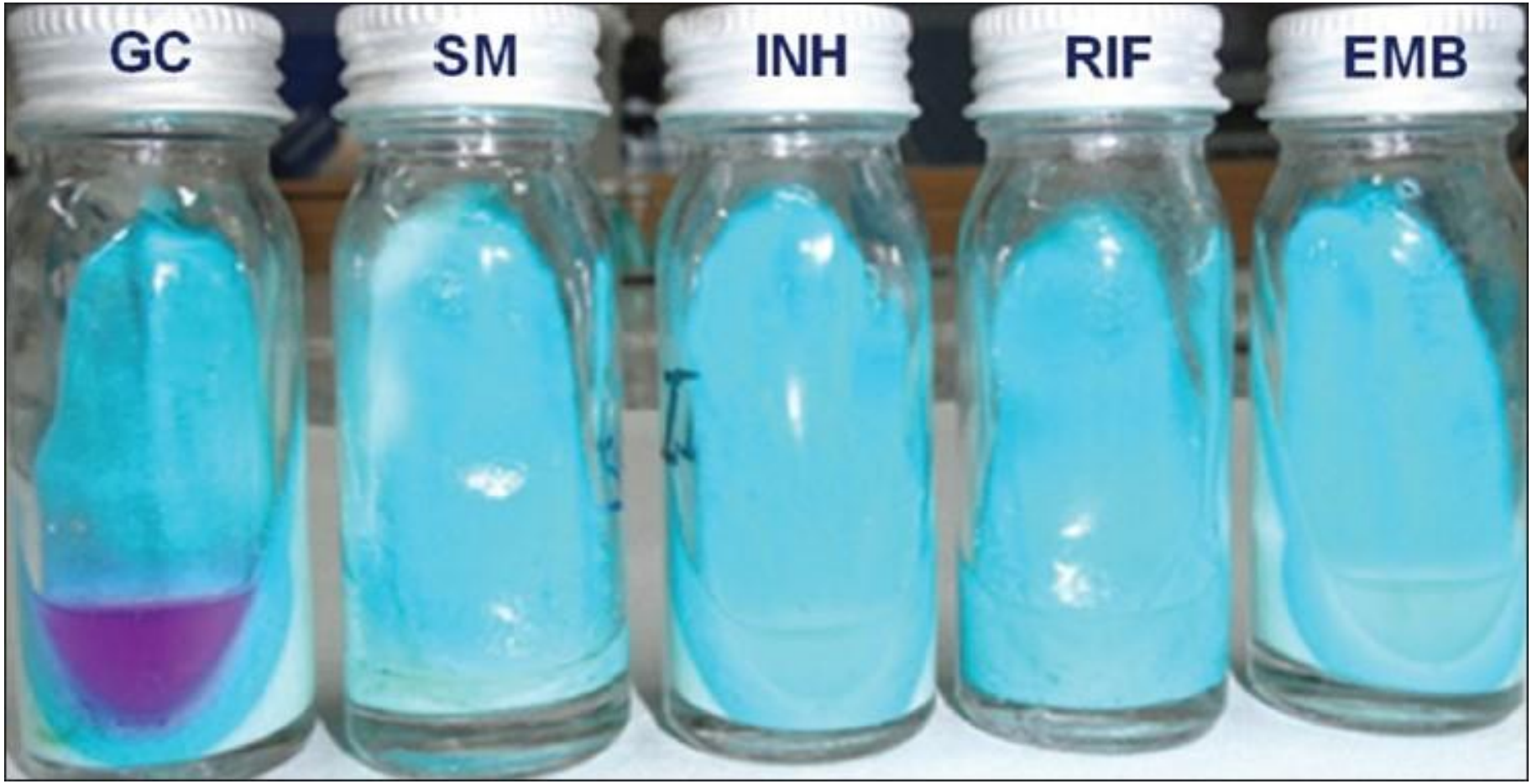
- Soli. However, solid media allow examination of colony morphology, detection of mixed cultures, and quantification of growth.

Drug Susceptibility Testing

- Testing of *M. tuberculosis isolates for drug susceptibility is important* to guide therapy.
- In the United States, the agar proportion method is most commonly used.

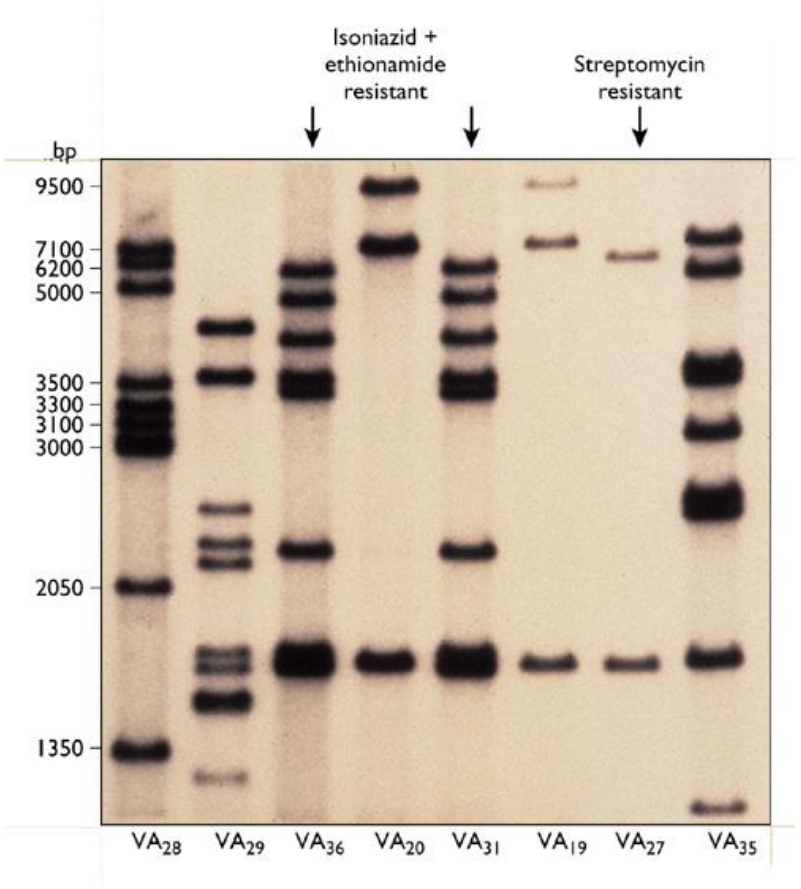


- Most useful are tests for RMP resistance, which predicts poor treatment outcomes and is a surrogate marker for MDR-TB.



Nucleic Acid Amplification

- Nucleic acid amplification tests (NAATs) offer another technique for the direct detection of *M. tuberculosis in clinical specimens.*
- The sensitivity of these NAATs is intermediate between acid-fast staining and culture.

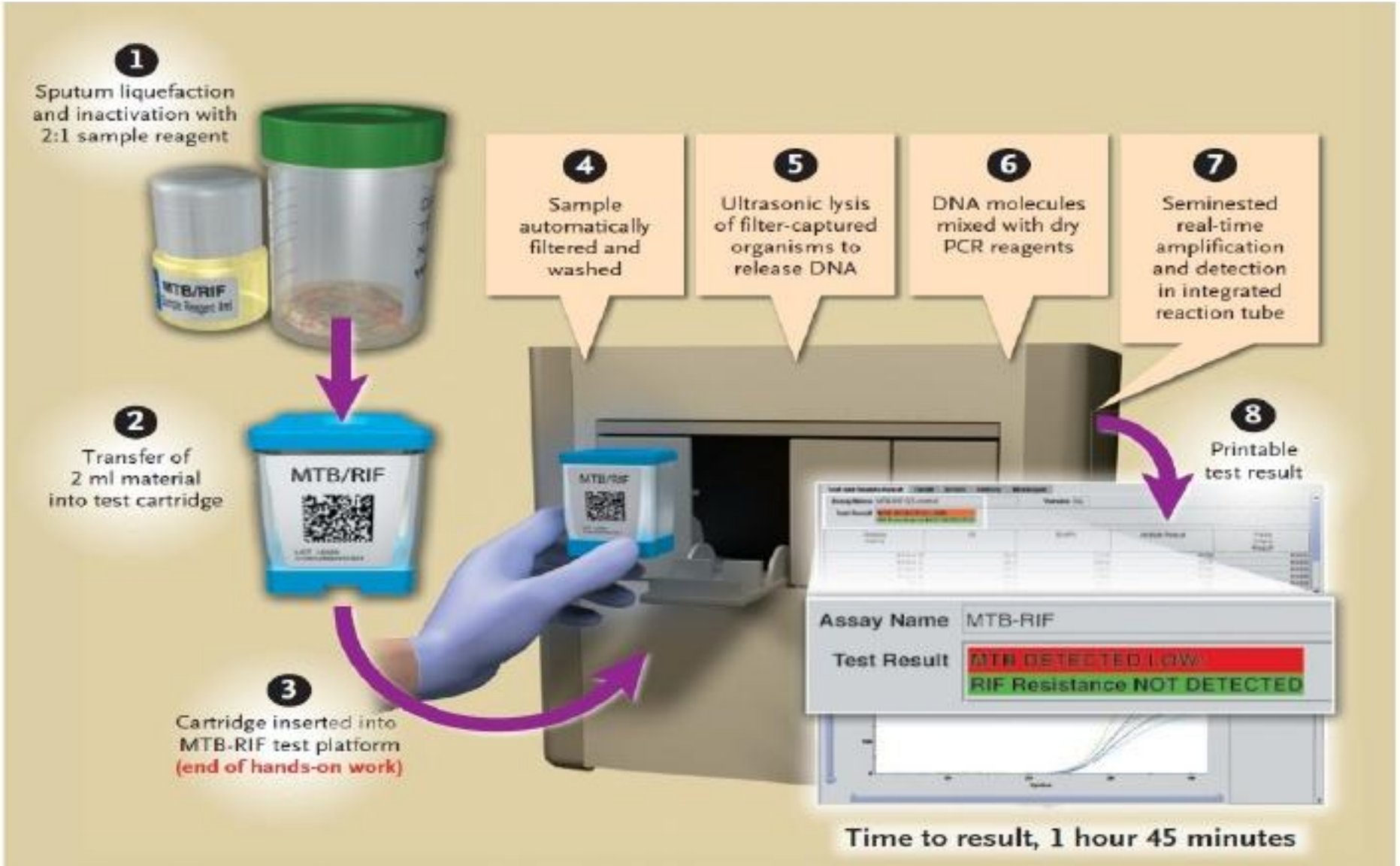


GeneXpert MTB/RIF

- *The GeneXpert* MTB/RIF is an automated molecular test for detection of *M. tuberculosis with sensitivity and specificity that* approaches culture.

- The test is simple to perform and gives results in 100 minutes. It uses real-time polymerase chain reaction (PCR) amplification of an *M. tuberculosis gene for detection.*

Xpert MTB/RIF



Xpert MTB/RIF assay

GeneXpert system

5	20	80	Samples per shift	500–1000

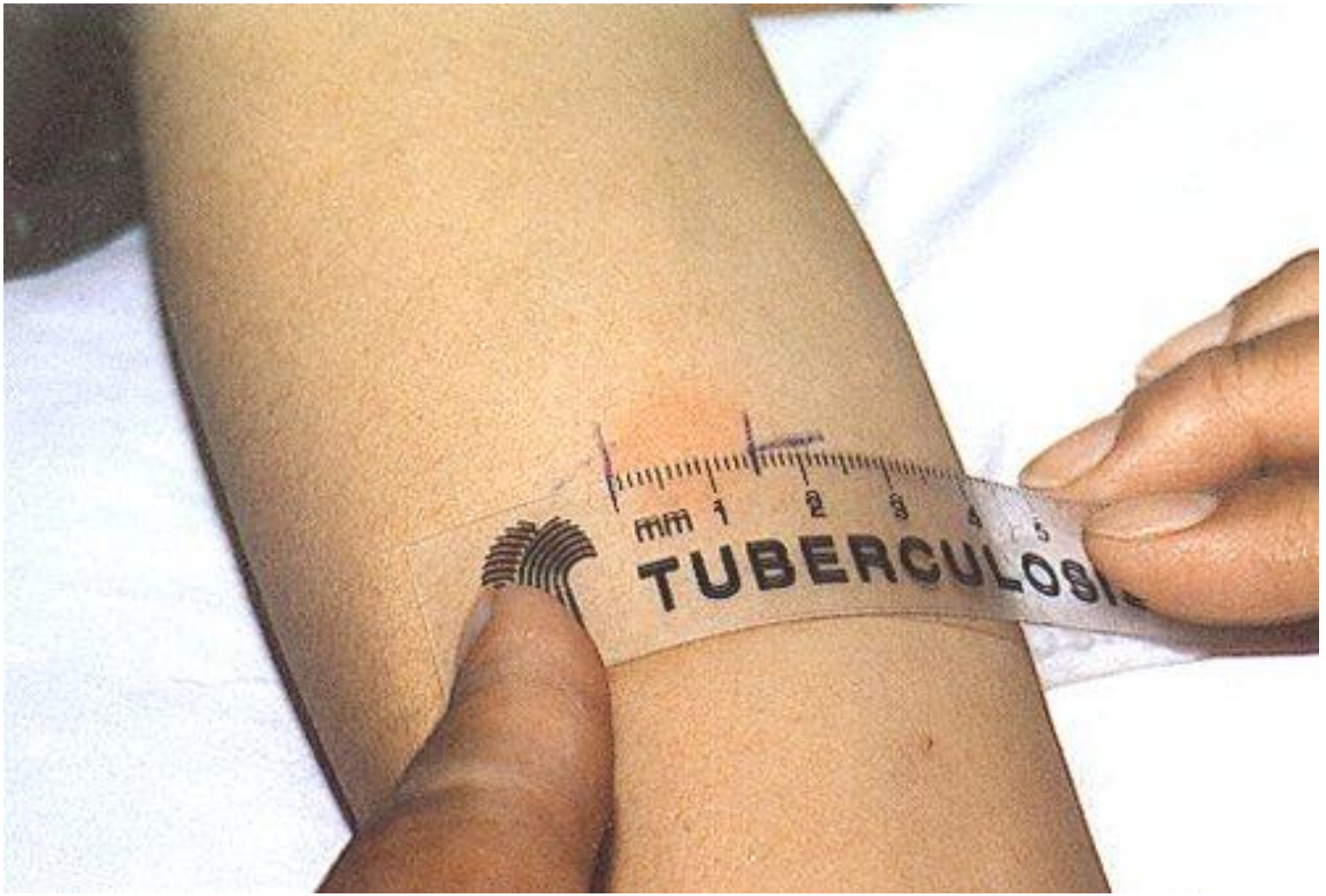
- *Analysis of three* sputum samples with GeneXpert MTB/RIF sensitivity **99.8% for smear and culture positive cases**

and **90.2% for smear negative culture-positive cases**.

- This assay simultaneously detects rifampin resistance
- The assay can also be used on nonrespiratory samples (e.g., pleural fluid, CSF, urine, fine-needle aspirates)

- We recommend performing rapid molecular drug susceptibility testing for rifampin with or without isoniazid of persons who are either AFB smear positive and who meet one of the following criteria:
- (1) have been treated for tuberculosis in the past
- (2) were born in or have lived for at least 1 year in a foreign country with at least a moderate tuberculosis incidence (≥20 per 100 000) or a high primary multidrug-resistant tuberculosis prevalence (≥2%),
- (3) are contacts of patients with multidrug- resistant tuberculosis
- (4) HIV infected

TUBERCULIN SKIN TEST


mm 1 2 3 4 5
TUBERCULOSI

Interpretation

- Based on sensitivity and specificity of tuberculin skin testing, three cutoff levels have been recommended for defining positive reactions,
- 5 mm, 10 mm, and 15 mm
- The 5-mm cut off is used for immunocompromised persons and recent contacts of patients with active tuberculosis.
- The 10-mm cutoff is used for other high-risk groups.
- The 15-mm cutoff is used for low-risk groups
- *Induration* of less than 10 mm may be cross-reactions caused by infection with other mycobacterial species or prior BCG vaccination.
- Unless BCG vaccination was very recent, positive tuberculin reactions should not be attributed to BCG.

False-Positive and False-Negative Reactions

False-positive reactions represent

- nontuberculous mycobacterial infection.

False-negative reactions occur in at least 20% of all persons

- Most false-negative test results in patients with
- tuberculosis are attributed to general illness and become positive 2 to 3 weeks after effective treatment is initiated.
- Protein malnutrition
- Sarcoidosis
- Intercurrent viral infections such asHIV-1 infection or vaccination with live-virus vaccines (measles, smallpox)
- Reticuloendothelial disease
- corticosteroid therapy

- TST results are negative during the first 3 to 9 weeks of initial infection.

Interferon-γ Release Assays for Latent *M. tuberculosis Infection*


TB Quantiferon TB Gold
3.0 mL
45.8
89.0
29.1
33.2
13.1
309
89.8
31.6
33.2
12.8
355
10:18
215
155
10:23

- While both IGRA and TST testing provide evidence for infection with Mtb, they **cannot distinguish active from latent TB.**
- Therefore, the diagnosis of active TB must be excluded prior to embarking on treatment for LTBI.

Antituberculosis Drugs

First-Line Drugs

- ***Isoniazid***
- ***Rifampin***
- ***Pyrazinamide***
- ***Ethambutol***
- ***Rifabutin****
- ***Rifapentine***

Second-Line Drugs

- ***Streptomycin***
- ***Cycloserine***
- ***p-Aminosalicylic acid***
- ***Ethionamide***
- ***Amikacin or kanamycin****
- ***Capreomycin***
- ***Levofloxacin****
- ***Moxifloxacin****
- ***Gatifloxacin****

Antituberculosis Drugs

I	Isoniazid	5	mg/kg
R	Rifampin	10	mg/kg
E	Ethambutol	15	mg/kg
S	Streptomycin	20	mg/kg
P	Pyrazinamide	25	mg/kg


۱۰۰ قرص خطدار
ایزونیازید ۱۰۰
هر وعده دارو را نیم تا یکساعت قبل
از غذا میل کنید.
دوره درمان را کامل کنید.
مصرف این دارورا قطع نکنید مگرطبق
دستورپزشک.
دردمای کمتر از ۳۰ درجه سانتیگراد
و دوراز نور نگهداری شود.
دارو را دور از دسترس اطفال قراردهید
فروش بدون نسخه پزشک ممنوع است
شماره پروانه ساخت: 086-DP
قیمت برای مصرف کننده: ۴۰۰۰ ریال
کارخانجات دارو پخش - ایران
۱۰۰ قرص خطدار
ایزونیازید ۳۰۰
دستور پزشک
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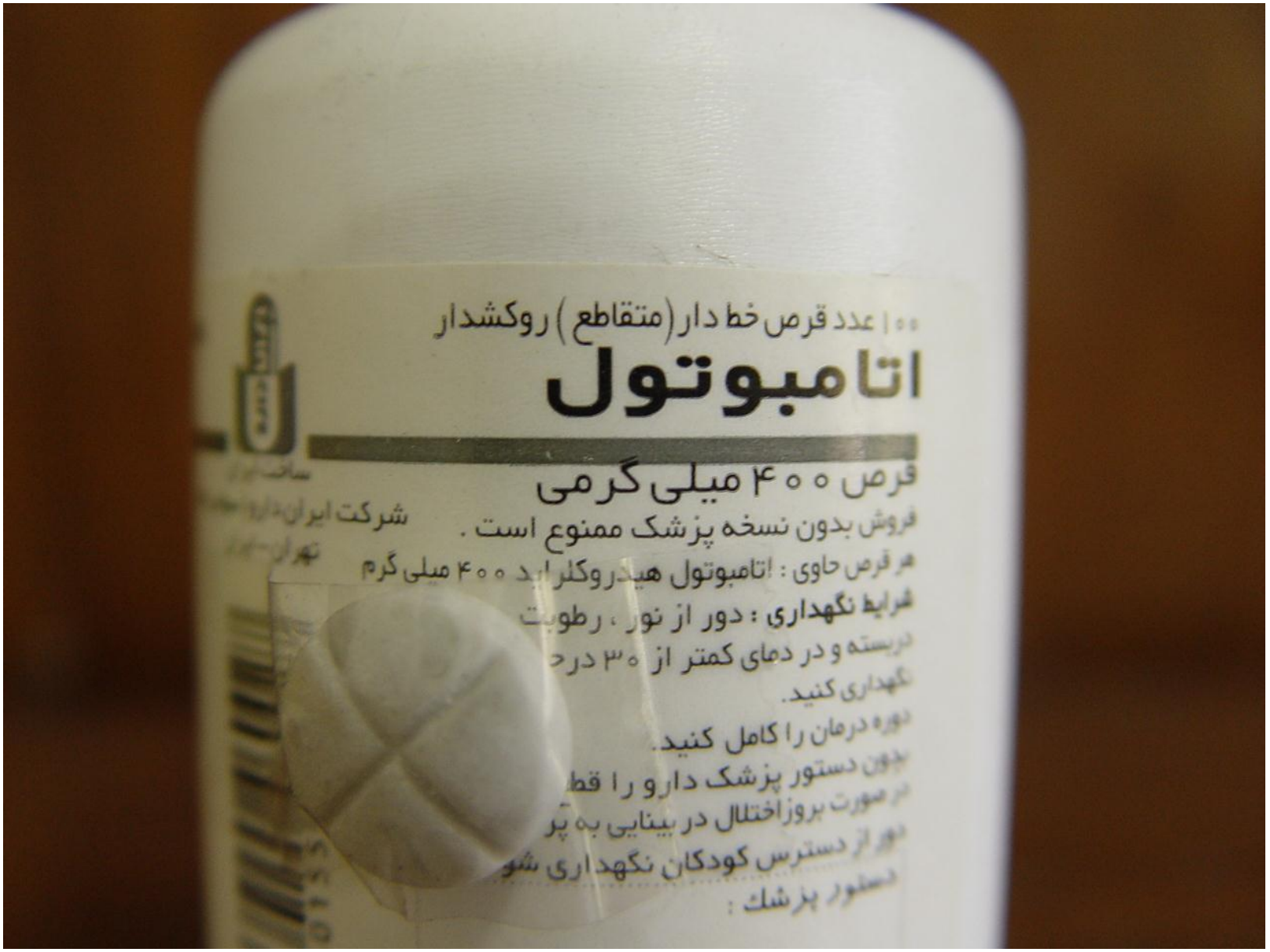
۱۰۰ کپسول
ریفامپین ۳۰۰
ساخت ایران
۱۰۰ کپسول
ریفامپین ۱۵۰


۰۰ | عدد قرص خط دار (متقاطع) روکشدار
اتامبوتول
قرص ۴۰۰ میلی گرمی
فروش بدون نسخه پزشک ممنوع است .
هر قرص حاوی : اتامبوتول هیدروکلراید ۴۰۰ میلی گرم
شرایط نگهداری : دور از نور ، رطوبت
دربسته و در دمای کمتر از ۳۰ درج
نگهداری کنید.
دوره درمان را کامل کنید.
بدون دستور پزشک دارو را قط
در صورت بروز اختلال در بینایی به پز
دور از دسترس کودکان نگهداری شو
دستور پزشک :


SAVA
Composition:
Each uncoated tablet contains:
Pyrazinamide BP 500 mg
Excipients q.s.
Storage:
Store in a cool and dry place.
Keep out of reach of children.
Dosage:
As directed by the Physician.
SAVA
10 X 10 Tablets
Pyrazinamide Tablets BP 500 mg

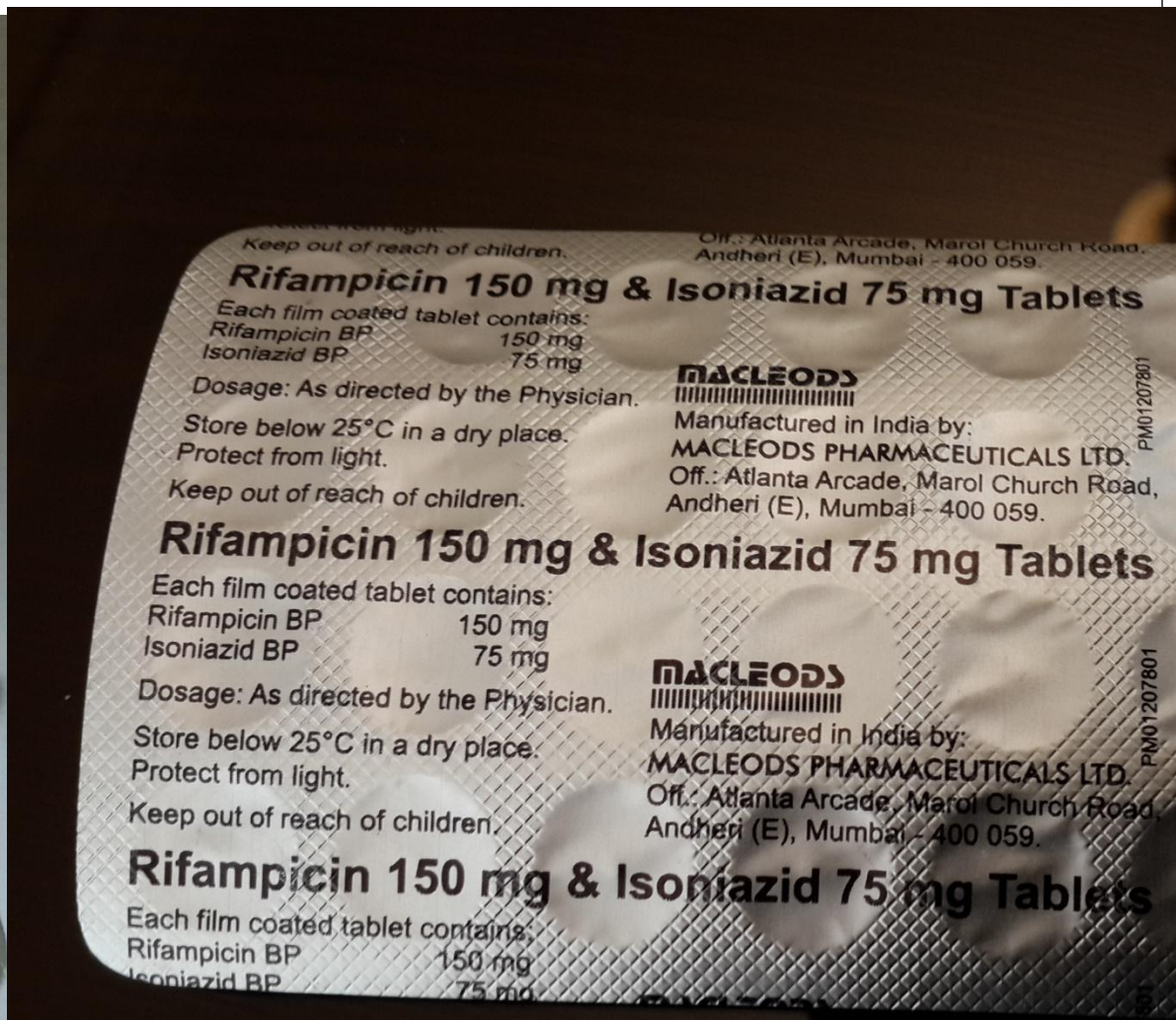

Streptomycin Sulfate
1000 mg (base)
For Injection
For I.M. Injection

Antituberculosis Drugs

I	Isoniazid	5 mg/kg	tab. 300mg
R	Rifampin	10 mg/kg	cap. 300mg
E	Ethambutol	15 mg/kg	tab.400mg
S	Streptomycin	20 mg/kg	vial.1gr
P	Pyrazinamide	25 mg/kg	tab.500mg

fixed-drug-combination

fixed-drug-combination



fixed-drug-combination

fixed-drug-combination


Fixed Dose
Combination
Separate
Pills

Common Adverse Reactions to Drug Treatment

Caused by	Adverse Reaction	Signs and Symptoms
Any drug	*Allergy*	*Skin rash*
Ethambutol	*Eye damage*	*Blurred or changed vision* *Changed color vision*
Isoniazid, *Pyrazinamide,* *or* *Rifampin*	*Hepatitis*	*Abdominal pain* *Abnormal liver function test results* *Fatigue* *Lack of appetite* *Nausea* *Vomiting* *Yellowish skin or eyes* *Dark urine*

Common Adverse Reactions to Drug Treatment

Caused by	Adverse Reaction	Signs and Symptoms
Isoniazid	Peripheral neuropathy	Tingling sensation in hands and feet
Pyrazinamide	Gastrointestinal intolerance	Upset stomach, vomiting, lack of appetite
	Arthralgia	Joint aches
	Arthritis	Gout (rare)
Streptomycin	Ear damage	Balance problems
		Hearing loss
		Ringing in the ears
	Kidney damage	Abnormal kidney function test results

Common Adverse Reactions to Drug Treatment

Caused by	*Adverse Reaction*	*Signs and Symptoms*
Rifamycins *Rifabutin* *Rifapentine* *Rifampin*	*Thrombocytopenia*	*Easy bruising* *Slow blood clotting*
	Gastrointestinal intolerance	*Upset stomach*
	Drug interactions	*Interferes with certain medications, such as birth control pills, birth control implants, and methadone treatment*

Drug Hepatitis

- ***The most common adverse reaction***
- ***Patients should be carefully educated about the signs and symptoms of drug-induced hepatitis (e.g., dark urine, loss of appetite)***
- ***and discontinue treatment promptly and see their health care provider***

biochemical monitoring is not routinely recommended, all adult patients should undergo baseline assessment of liver function

Older patients, those with concomitant diseases, those with a history of hepatic disease, and those using alcohol daily should be monitored especially closely (i.e., monthly), with repeated measurements of aminotransferases, during the initial phase of treatment.

- ***For patients with symptomatic hepatitis***
- ***and those with marked (five- to six fold) elevations in serum levels of aspartate aminotransferase,***

treatment should be stopped and drugs reintroduced one at a time after liver function has returned to normal.

indication for permanent discontinuation

- **Gouty arthritis due to pyrazinamide**

(Hyperuricemia and arthralgia caused by pyrazinamide can usually be managed by the administration of acetylsalicylic acid)

Autoimmune thrombocytopenia secondary to rifampin

- **Optic neuritis with ethambutol**

Treatment of Culture-Positive TB

Initial Phase

2 months - INH, RIF, PZA, EMB daily

(56 doses, within 8 weeks)

Continuation Phase

4 months - INH, RIF daily

(126 doses, within 18 weeks)

When to Extend Continuation-Phase Treatment for 3 Months?

- ***Cavitary pulmonary disease and positive sputum cultures at completion of initial phase***
- ***HIV-infected with positive 2-month sputum culture***

- ***To prevent isoniazid-related neuropathy, pyridoxine (10–25 mg/d) should be added to the regimen given to persons at high risk of vitamin B6 deficiency (e.g., alcoholics; malnourished persons; pregnant and lactating women; and patients with conditions such as chronic renal failure, diabetes, and HIV infection, which are also associated with neuropathy).***

- ***New smear- or culture-positive cases***
  2 HRZE 4 HR

- ***Pregnancy***
  2 HRE 7 HR

- ***Drug intolerance to Z***
  2 HRE 7 HR

- ***Resistance (or intolerance)to H***

Throughout (6-9) RZE

- ***Resistance (or intolerance) to R***

Same as for MDR-TB

treatment failure

Drug-Resistant TB

- rates of primary resistance are generally low, and isoniazid resistance is most common
- worldwide, MDR-TB is an increasingly serious problem in some regions***Resistant at least in two bactericidal drugs***
- **XDR-TB** due to **MDR** strains that are resistant to all **fluoroquinolones** and to at least one of three second-line injectable agents (**amikacin, kanamycin, and capreomycin**

SPECIAL CLINICAL SITUATIONS

- ***most forms of disease can be treated with the 6-month regimen like recommended for patients with pulmonary disease.***
- ***Bone and joint tuberculosis, tuberculous meningitis, or miliary tuberculosis receive 9 to 12 months of treatment.***
- ***Silicotuberculosis necessitates the extension of therapy by at least 2 months***

Renal failure

- Dosages of INH and RMP need **not** be adjusted for renal failure but should be administered after dialysis,
- pyridoxine supplementation should be routine
- In patients with creatinine clearance less than 30 mL/min and those on hemodialysis, EMB should be dosed at 15 to 25 mg/kg
- PZA at 25 to 35 mg/kg,
- both given **three times per week**
- (after dialysis for those on hemodialysis).

Hepatic disease

- The selection and dosage of antituberculous agents do **not** need to be modified in most patients with underlying liver disease, but hepatic aminotransferase and bilirubin levels must be **followed closely**.
- For persons with extensive tuberculosis and severe hepatitis who should not have a prolonged treatment interruption**, "bridging" regimens** that include EMB, fluoroquinolone, and STM could be considered until a more standard regimen can be instituted.

Influence of Chemotherapy on Spread of Infection

- The time required to become noninfectious depends on the patient's burden of organisms, but there is indirect evidence that this **occurs within 2 weeks** in patients with drug-sensitive tuberculosis.
- CDC in 1994 established very stringent criteria for removing patients from respiratory isolation, which now include
- **Three consecutive negative sputum smears** on specimens obtained **at least 8 hours apart**.