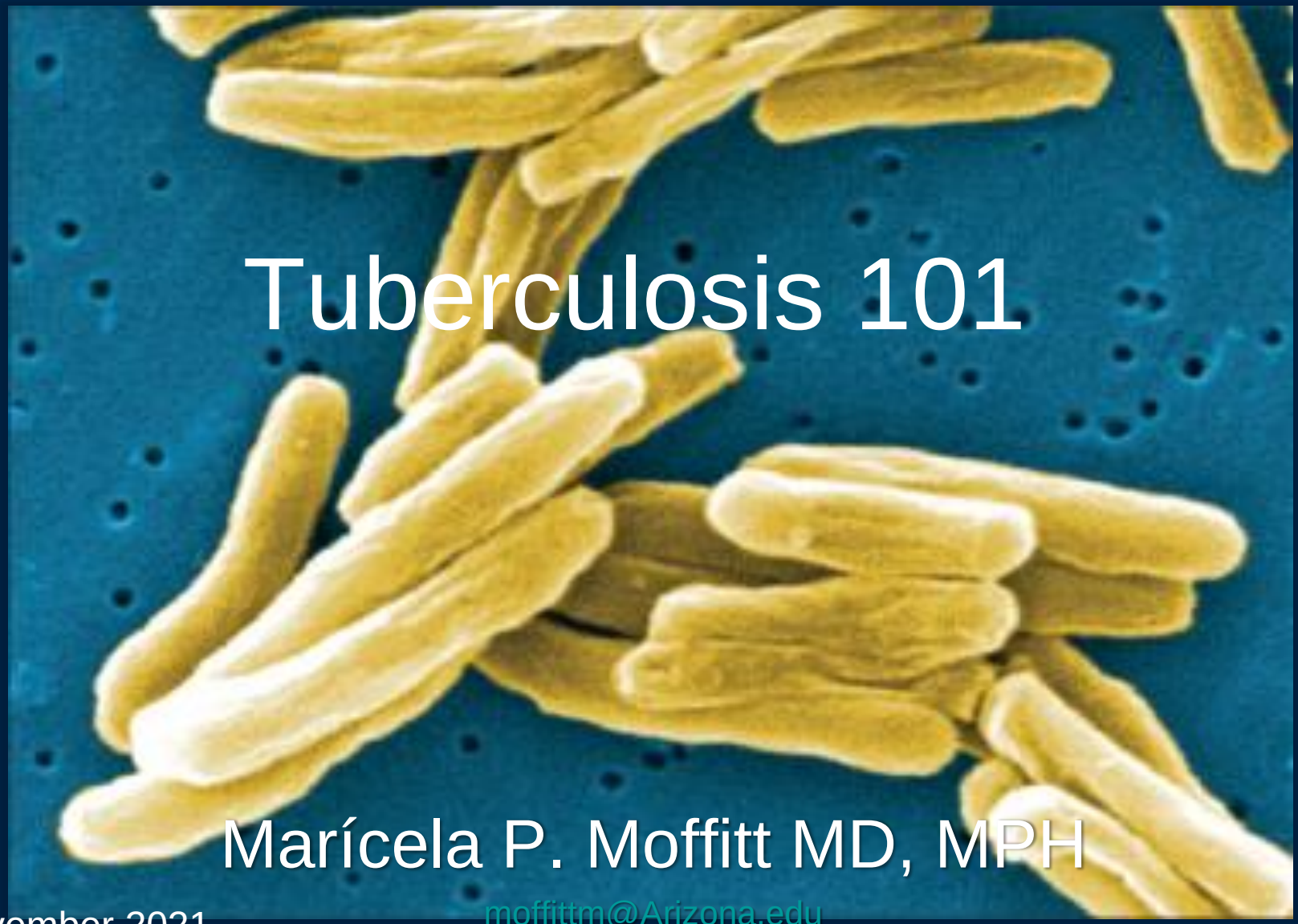

Tuberculosis 101

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Learning Objectives

- Understand the distinction between the risk of acquiring the infection and progression to disease
- Discuss the pathogenesis of TB and the effect of disease progression in specific risk groups

- Describe the common clinical manifestations of active TB infection
- Describe the gold standard for diagnosis of active pulmonary TB infection.

Learning Objectives

- Describe the two testing options used for the diagnosis of TB infection.
- Justify the need for 4 drugs in the intensive phase of TB treatment.
- List appropriate Rx for LTBI
- Identify the most common toxicities seen with Rx
- Discuss the appropriate application of isolation, empiric treatment and monitoring.

Terminology

Exposure

Implies significant contact with a adult or adolescent with suspected or confirmed TB

Tuberculin Skin Test (TST) is negative

Interferon-Gamma Release Assays (IGRAs) is negative

Terminology

Infection: Primary Disease, TB Infection, Latent TB Infection, LTBI

Bacteria dormant in body

Inhalation> Phagocytosis> lymphohematogenous disseminated

no symptoms

Tuberculin Skin Test (TST) is positive

Interferon-Gamma Release Assays (IGRAs) is positive

Rx called chemoprophylaxis, preventative therapy or treatment of LTBI

Terminology

Disease

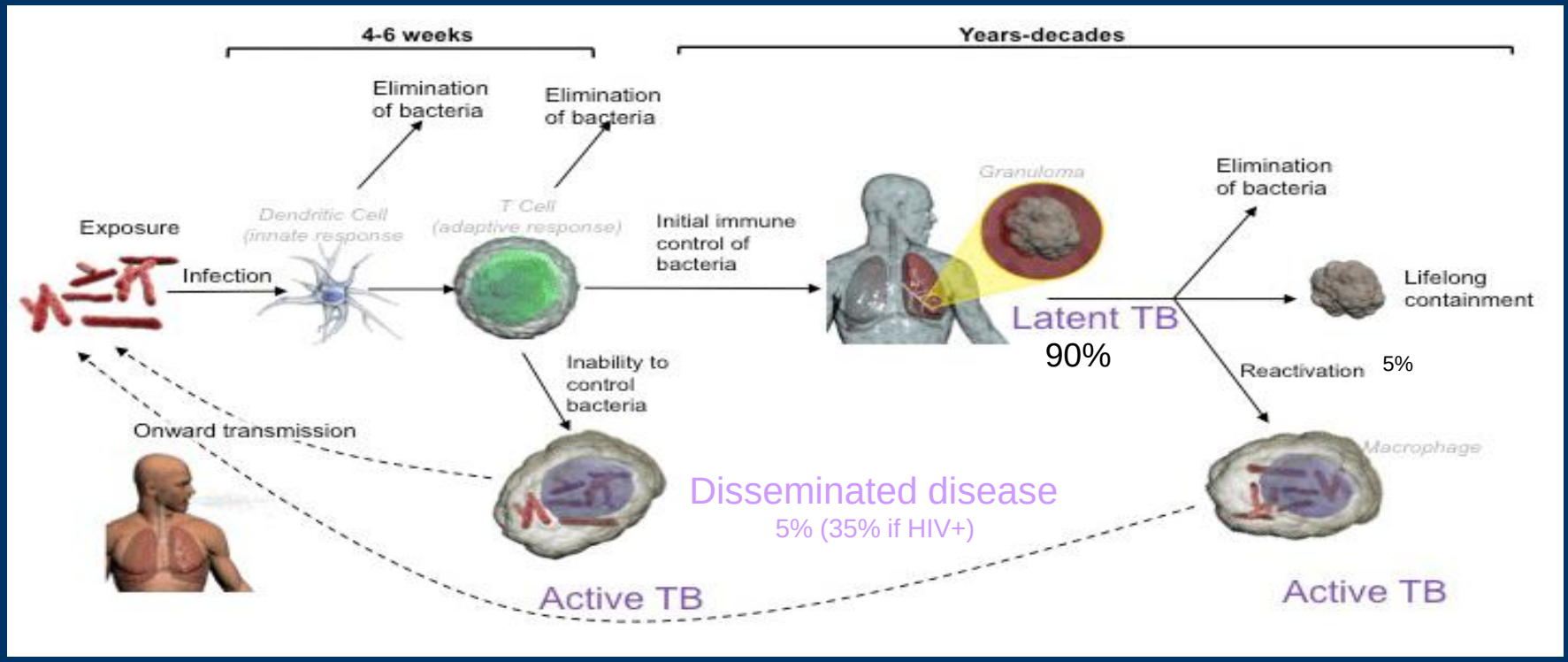
Occurs when signs or symptoms or radiographic manifestations caused by MTB become apparent

TB Tuberculosis Active TB Reactivated TB or Disseminated

Tuberculin Skin Test (TST) maybe positive

Interferon-Gamma Release Assays (IGRAs) maybe positive

Natural History



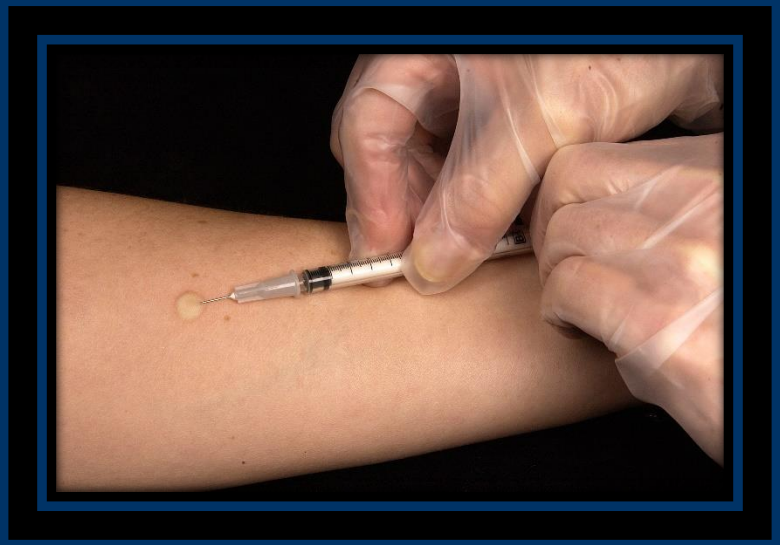
Risk Factors for acquiring *M. tuberculosis* infection

- Close contacts to case or suspect with TB
- Foreign-born persons from areas of high incidence of TB (e.g., Africa, Asia, Eastern Europe, Latin America, and Russia)
- Persons who visit areas with a high prevalence of active TB
- Residents and employees of congregate settings whose clients are at increased risk for active TB (e.g., correctional facilities, LTC facilities, and homeless shelters)
- HCW who serve clients who are at increased risk for active TB;
- medically underserved, low-income populations, or persons who abuse drugs or alcohol
- infants, children, and adolescents exposed to adults who are at increased risk for latent *M. tuberculosis* infection or active TB

Source: Based on CDC. Targeted tuberculin testing and treatment of latent tuberculosis infection. MMWR 2000;49(No. RR-6).

Testing for TB Infection

Interferon Gamma Release Assays (IGRA)
QuantiFERON /T-spot



TB Skin Test (TST)

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Which one to use?

Group	Testing Strategy	Considerations
Likely to be Infected **High** Risk of Progression (TST ≥ 5mM)	**Adults** **Acceptable**: IGRA OR TST Consider dual testing where a positive result from either result would be considered **positive** **Children ≤ 5 years of age** **Preferred**: TST **Acceptable**: IGRA OR TST Consider dual testing where a positive result from either would be considered **positive**[1]	Prevalence of BCG vaccination Expertise of staff and/or laboratory Test availability Patient perceptions Staff perceptions Programmatic concerns
Likely to be Infected **Low** to **Intermediate** Risk of Progression (TST ≥ 10mM)	**Preferred**: IGRA where available **Acceptable**: IGRA or TST	
Unlikely to be Infected (TST > 15mM)	**Testing for LTBI is not recommended** **If necessary:** **Preferred:** IGRA where available. **Acceptable**: Either IGRA OR TST **For serial testing**: **Acceptable**: Either IGRA OR TST Consider repeat or dual testing where a negative result from either would be considered **negative**[2]	

Mantoux tuberculin skin test

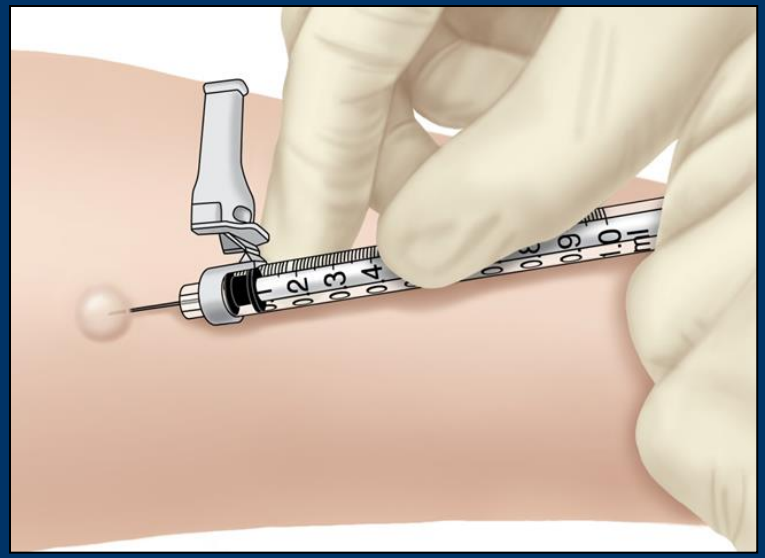
Purified Protein Derivative (PPD)

- Problems:
  - Administration
  - Interpretation
  - Tuberculin Antigen
  - Host Response

- False Negatives
- False Positives

Administering the TST

Inject 0.1 ml of 5 TU PPD tuberculin intradermal on volar surface of forearm (using a 27-guage needle)



Produce a wheal 6 to 10 mm in diameter

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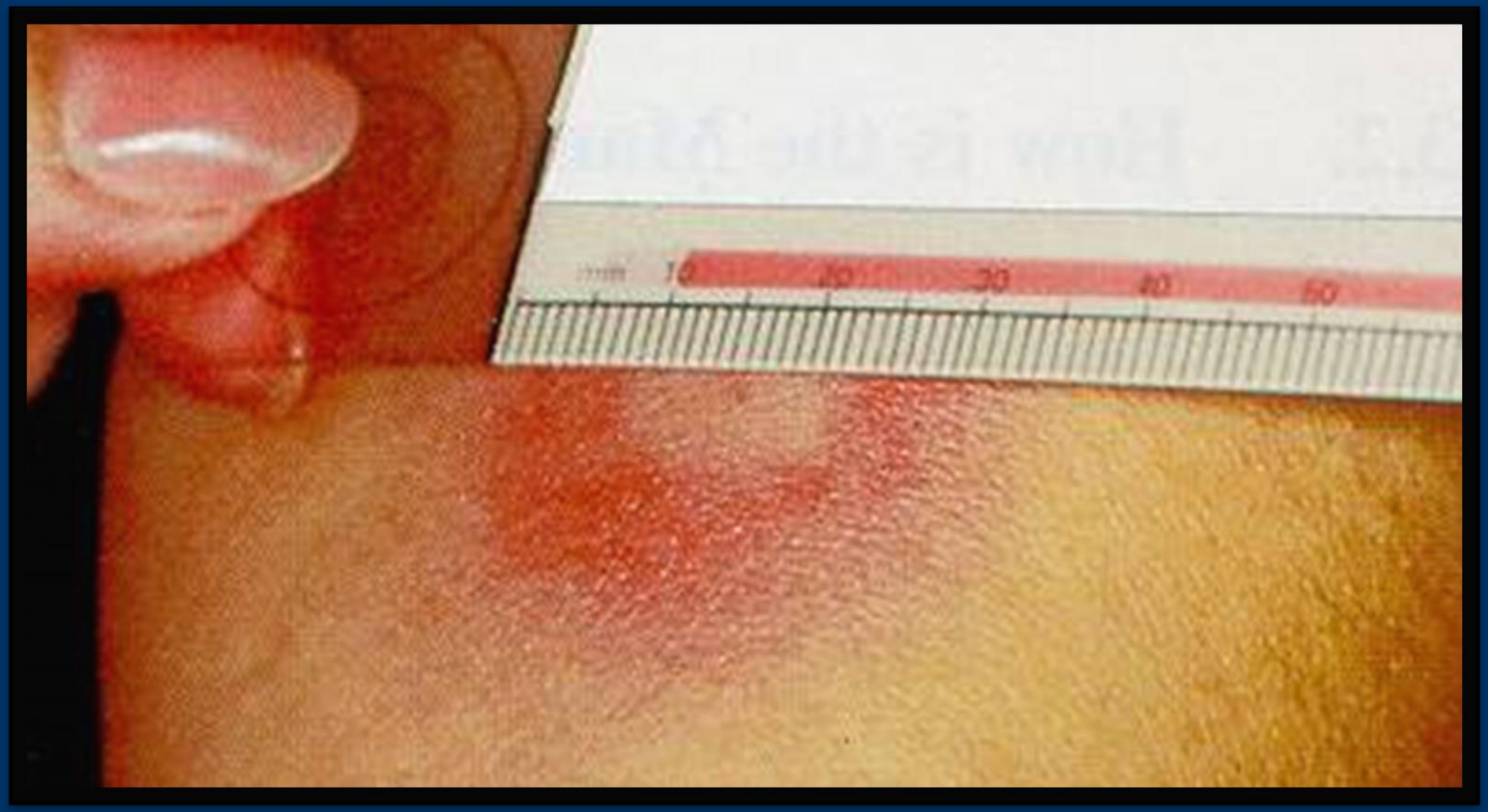
Reading a tuberculin skin test



Measure reaction in 48 to 72 hours
Measure induration, not erythema
Record reaction in millimeters, not “negative” or “positive”

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Interferon-Gamma Release Assays (IGRAs)

- Whole-blood test used to detect
  M. tuberculosis infection
- Two FDA approved IGRAs are commercially available in the US:
  - QuantiFERON® -TB Gold-in-tube test (QFT-GIT)
  - T.SPOT® .*TB* test (T-Spot)

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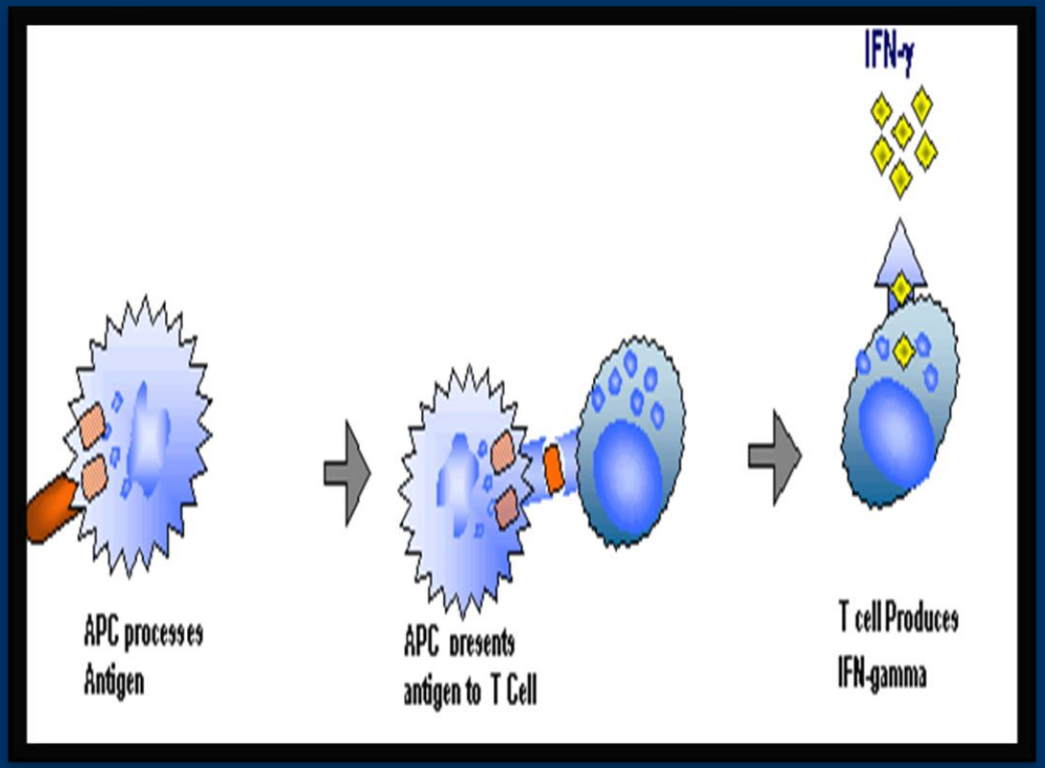
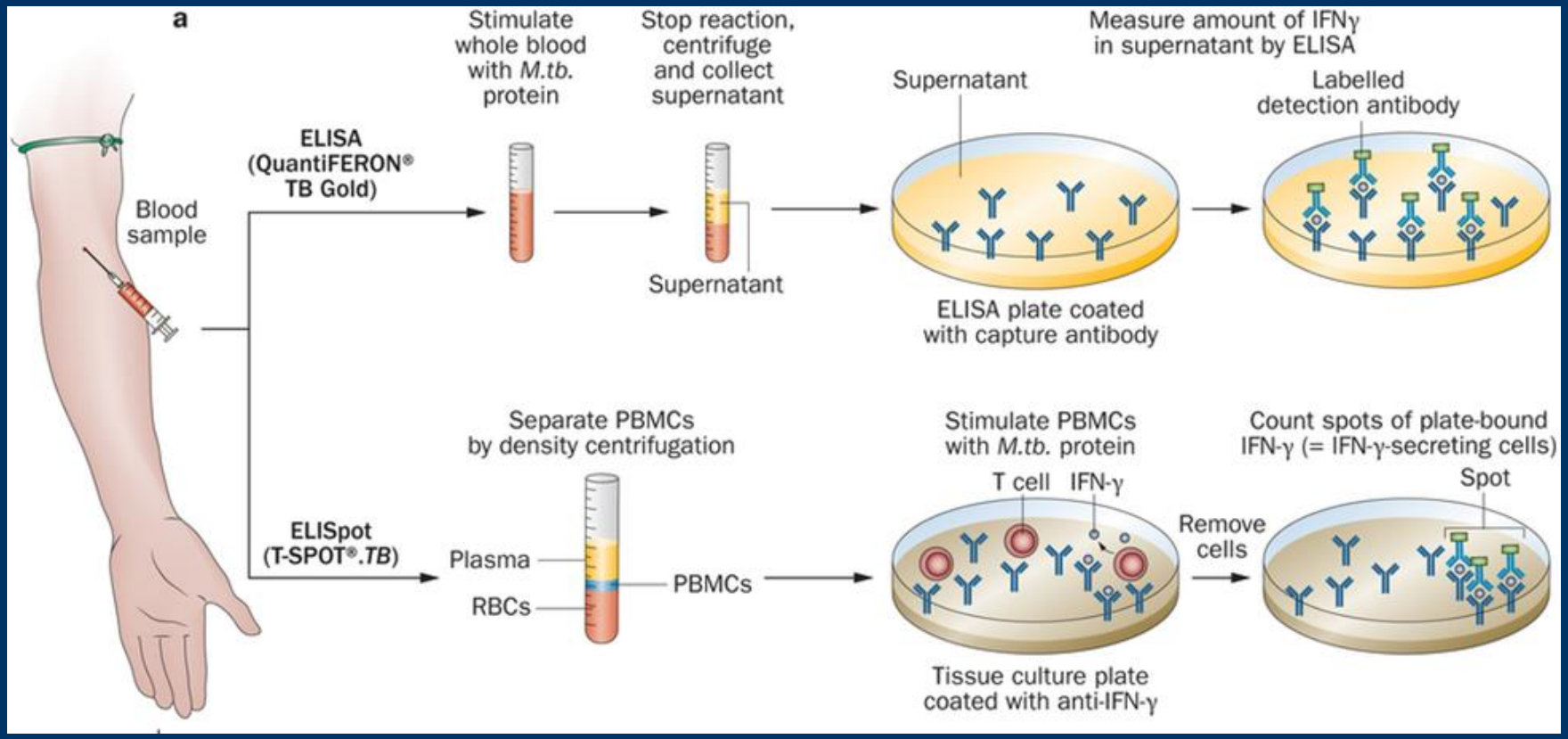
Cell Mediated Response

in vitro

- Antigen is added to a whole blood sample
- Memory T-cells are stimulated when APCs processed TB proteins.
- This results in the rapid secretion of cytokines and cytotoxins, in an attempt to control the infection.
- IFN-gamma is one cytokine that is produced





Mycobacterium tuberculosis IFN-γ-release assay. In the ELISA method (marketed as QuantiFERON®-TB Gold In-Tube Test), whole blood is stimulated with *M. tuberculosis* proteins, and the amount of IFN-γ secreted into the supernatant is quantified by ELISA.[69]

In the ELISPOT method (marketed as T-SPOT.*TB*; Oxford Immunotec, UK),[68] PBMCs are prepared by density gradient centrifugation. A defined number of cells is then stimulated with *M. tuberculosis* protein for 24 h on plates coated with anti-IFN-γ antibodies. Antigen-responsive cells secrete IFN-γ, which binds to these antibodies and is, after removal of the cells, subsequently detected by a second labelled anti-IFN-γ antibody. The number of spots on the plate corresponds to the number of IFN-γ^+ cells in the sample.

Ermann, J. *et al.* (2015) Immune cell profiling to guide therapeutic decisions in rheumatic diseases *Nat. Rev. Rheumatol.* doi:10.1038/nrrheum.2015.71

Criteria for classifying +

>= 5mm or IGRA+	>= 10 mm or IGRA+	>= 15 mm or IGRA+
HIV-infected persons	Recent immigrants (< 5 years) from high-prevalence countries	with no known risk factors for TB.
Recent contact	IVDA	
Fibrotic changes on Chest radiograph consistent w/ prior TB	Residents and employees of high-risk congregate settings	
Organ transplants	Mycobacteriology laboratory personnel	
Imunosuppressed w/ >15 mg/day of prednisone for 1 month or Rx TNF-a antagonists	Persons with clinical conditions that place them at high risk: -DM, silicosis, gastrectomy, 10%< IBW, ESRD, head &neck CA, hematologic CA, smokers, ETOH	
	Children < = 4 years of age	
	Infants, children, adolescents exposed to high-risk adults	

Annals of IM Feb 7, 2017

Calculator | About | Disclaimer | References | Links

The Online TST/IGRA Interpreter

Version 3.0

The following tool estimates the risk of active tuberculosis for an individual with a tuberculin skin test reaction of ≥5mm, based on his/her clinical profile. It is intended for adults tested with standard tuberculin (5 TU PPDS, or 2 TU RT-23) and/or a commercial Interferon Gamma release assay (IGRA). For more details about the algorithm used, go to the About page. The current version of the algorithm contains modifications of the original version, which was detailed in a paper by Menzies, et al. (2008). For further information see references, or contact dick.menzies@mcgill.ca

Please select the best response for each field:

TST Size: 5-9 mm

IGRA Result: IGRA Not Done

Age: 36

Age at immigration (if person immigrated to a low TB incidence country): N/A

Country of birth: United States of America

State: Arizona

Race/ethnicity: White/Caucasian

BCG status: Never vaccinated or unknown

For more info, visit: BCG World Atlas.

Recent contact with active TB: No Contact

Please select all the conditions that currently apply to the patient:
(If none of these conditions apply, please leave boxes unchecked)

- [ ] AIDS
- [ ] Abnormal chest x-ray: fibronodular disease
- [ ] Chronic renal failure requiring hemodialysis
- [ ] Diabetes Mellitus (all types)
- [ ] Recent TB infection (TST conversion ≤ 2 years ago)
- [ ] Silicosis
- [ ] Tumor Necrosis Factor (TNF)-alpha inhibitors(e.g.
- [ ] Abnormal chest x-ray: granuloma
- [x] Carcinoma of head and neck
- [ ] Cigarette smoker(>1 pack/day)
- [ ] HIV infection
- [ ] Transplantation (requiring immune-suppressant therapy)
- [ ] Treatment with glucocorticoids
- [ ] Underweight (< 90 per cent ideal body weight or a

Results

Printable version

Below are the results for a patient with a TST reaction of **5-9 mm**, who is **36** years old, born in **USA, Arizona**, whose BCG status is **Never vaccinated or unknown**, who has had **no contact** with active TB, and who can be characterized by:

- **Carcinoma of head and neck**
- **White/Caucasian**

The likelihood that this is a true positive test (PPV) is: **36.85%**

The annual risk of development of active tuberculosis disease is estimated to be **0.59%**.

The cumulative risk of active tuberculosis disease, up to the age of 80, is: **25.94%**

If treated with INH, the probability of clinically significant drug-induced hepatitis is **1.2%**, and the associated probability of hospitalization related to drug-induced hepatitis is **0.2%**.

Refresh

http://www.tstin3d.com/en/calc.html

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Groups with Increased Likelihood of Infection with Mtb	Benefit of Therapy	LTBI Testing Strategy	
Household contact or recent exposure of an active case	Yes	Likely to be Infected Low to Intermediate Risk of Progression (TST ≥ 10mM)	Likely to be Infected High Risk of Progression (TST ≥ 5mM)
Mycobacteriology laboratory personnel	Not demonstrated		
Immigrants from high burden countries (>20 / 100,000)	Not demonstrated		
Residents and employees of high risk congregate settings	Yes		
None	Not demonstrated	Unlikely to be Infected (TST > 15mM)	

Risk of Infection ↑

Risk of Developing Tuberculosis if Infected →

Low	Intermediate (RR 1.3 -3)	High (RR 3-10)
No risk factors	Clinical predisposition Diabetes Chronic renal failure Intravenous drug use	Children age less than 5 HIV infection Immunosuppressive therapy Abnormal CXR consistent with prior TB Silicosis

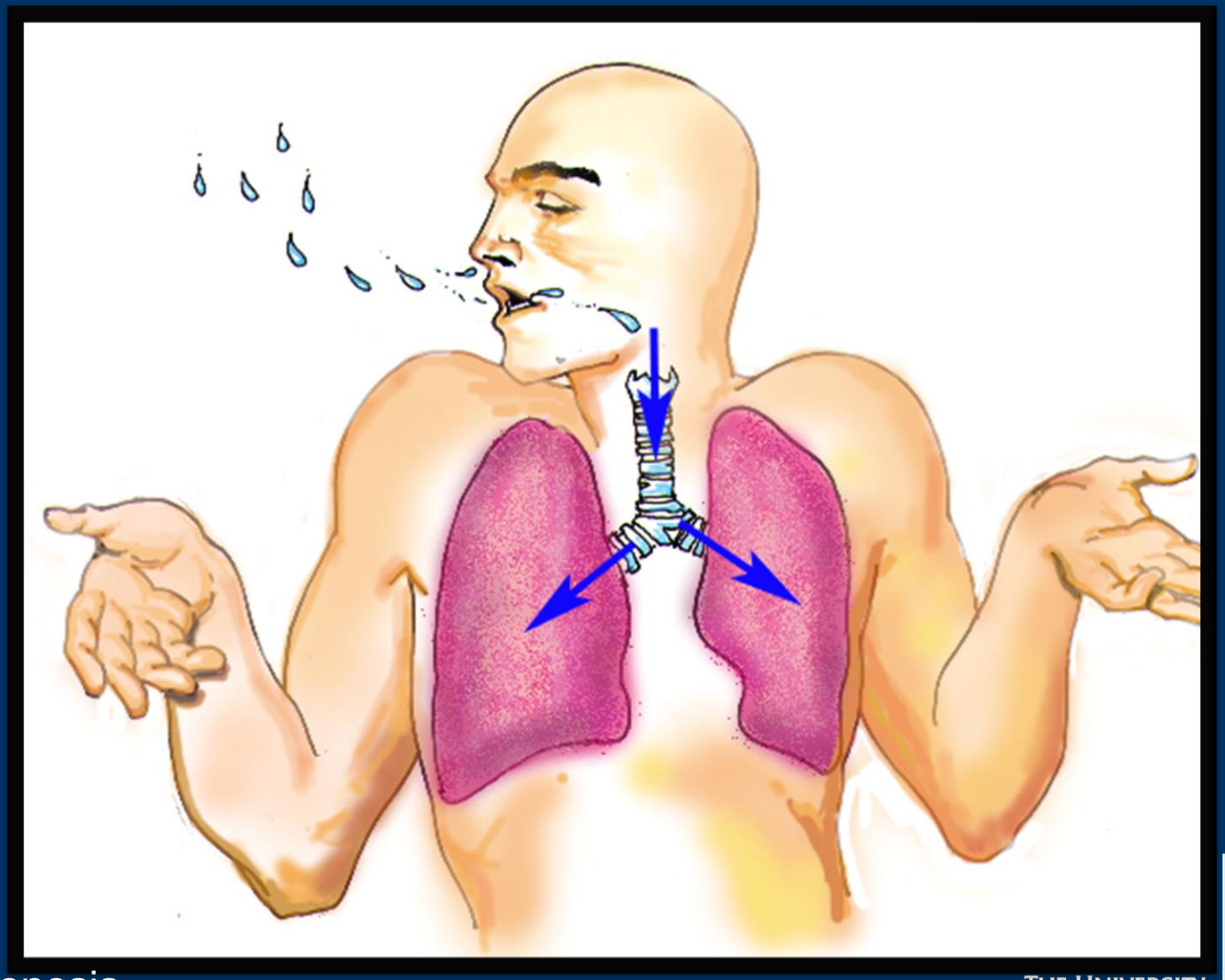
Benefit of Therapy	
Not demonstrated	Yes

Pathogenesis

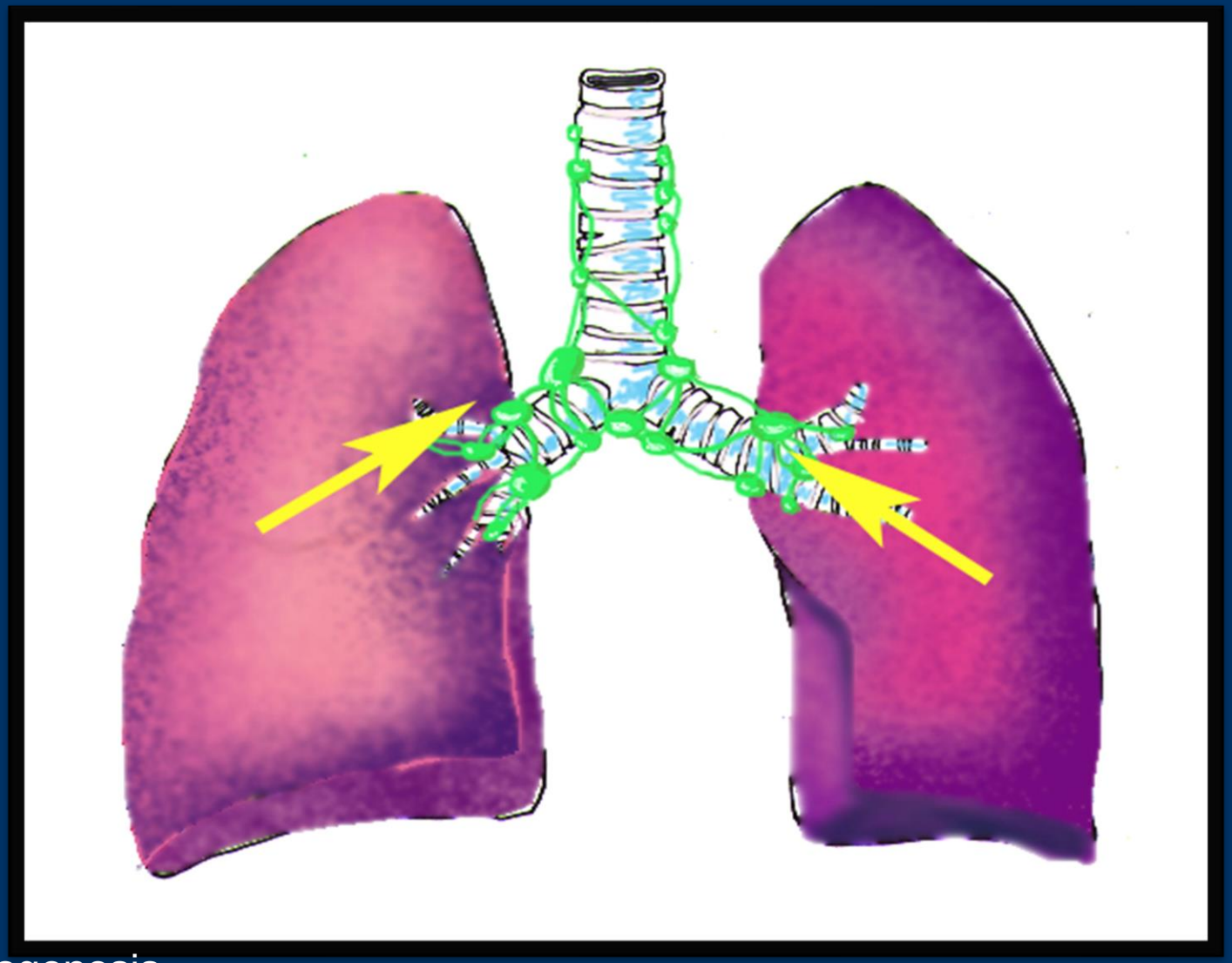
TB Exposure ->TB infection ->
TB disease

Primary Infection

Droplet nuclei
3-5µ



Primary Infection



Pathogenesis

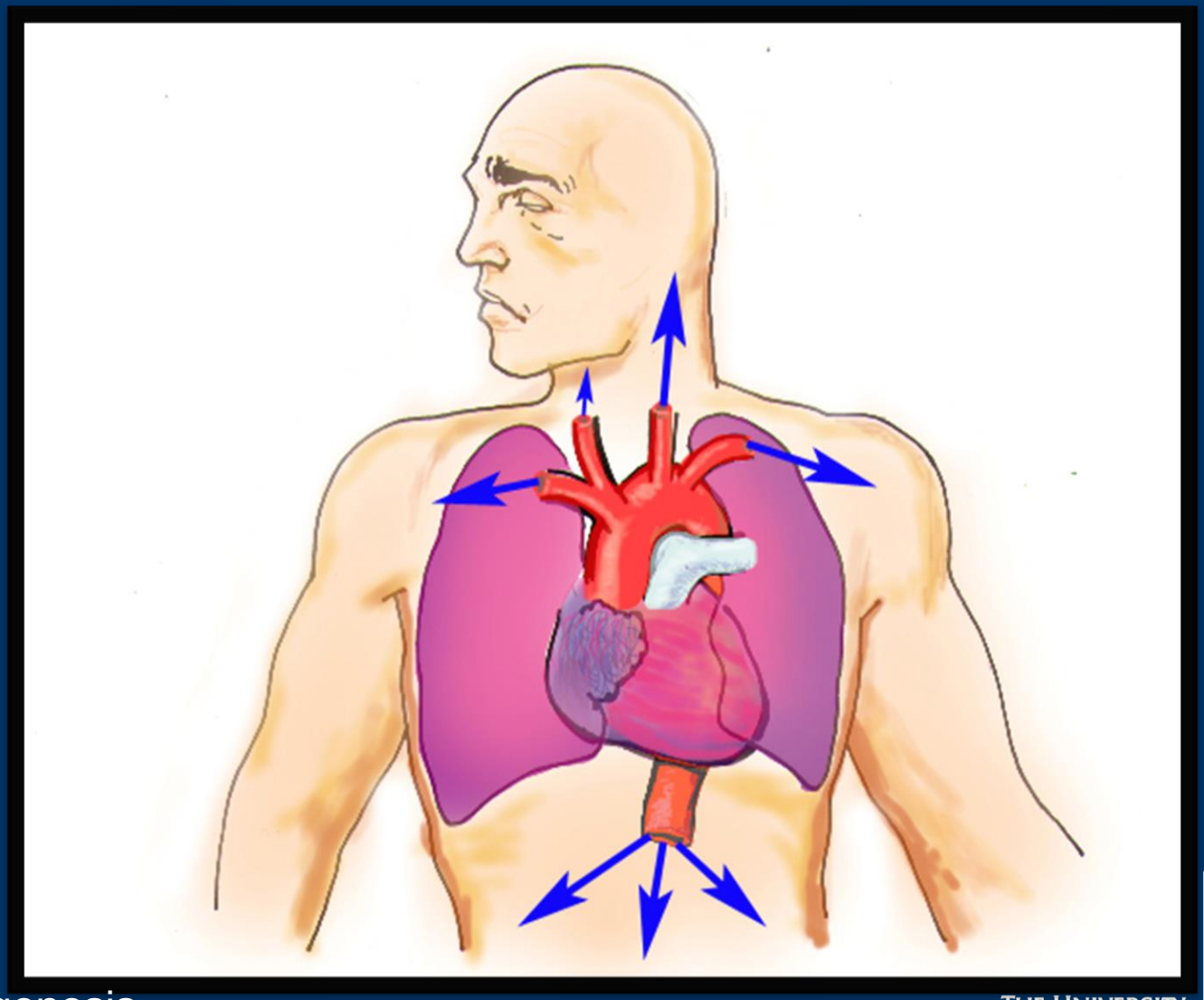
Virulent factors

Inhib macrophage maturation,
induce release of TNF
Sulfatides (surface glycolipids prevent Phagolymsomal fusion

Ghon Complex:

Calcified hilar Node and calcified Granuloma in mid to lower lung fields.

Primary Infection



Risk factors for progression of infection to active tuberculosis

- HIV infection
- infants and children aged <5 years
- receiving immunosuppressive therapy such as TNF-α antagonists, steroids ≥15 mg of prednisone per day, or Rx following transplantation
- recently infected with TB (within the past 2 years);
- history of untreated or inadequately treated active TB, including persons with fibrotic changes on chest radiograph consistent with prior active TB
- persons with silicosis, DM, CKD, leukemia, lymphoma, or cancer of the head, neck, or lung;
- persons who have had a gastrectomy or jejunoileal bypass;
- persons who weigh <90% of their ideal body weight;
- cigarette smokers and persons who abuse drugs or alcohol
- medically underserved or low-income populations

Source: Based on CDC. Targeted tuberculin testing and treatment of latent tuberculosis infection. MMWR 2000;49(No. RR-6).

The sleeping giant

TUBERCULOSIS: LATENT

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Latent TB Infection Treatment Regimens

Drugs	Duration	Interval	Comments
Isoniazid and Rifapentine	3 months	Once weekly*	Not recommended for persons who are: • Less than 2 years old, • Living with HIV/AIDS and taking antiretroviral medications with clinically significant or unknown drug interactions with rifapentine, • Presumed infected with INH- or RIF-resistant M. tuberculosis, and • Women who are pregnant or expect to become pregnant within the 12 week regimen.
Isoniazid and Rifampin		Daily	
Rifampin	4 months	Daily	Not recommended for persons who are: • Living with HIV/AIDS and taking antiretroviral medications with clinically significant or unknown drug interactions with rifampin (rifabutin may be used as a substitute), • Presumed infected with RIF-resistant M. tuberculosis, and • Women who are pregnant or expect to become pregnant within the 4 month regimen.
Isoniazid	6 months	Daily	Not recommended for persons who are presumed infected with INH-resistant M. tuberculosis.
		Twice weekly**	Not recommended for persons who are presumed infected with INH-resistant M. tuberculosis.
Isoniazid	9 months	Daily	Not recommended for persons who are presumed infected with INH-resistant M. tuberculosis. Preferred treatment for: • Persons living with HIV AIDS and taking antiretroviral medications with clinically significant or unknown drug interactions with once-weekly rifapentine or daily rifampin, • Pregnant women (with pyridoxine/vitamin B6 supplements)
		Twice weekly**	Not recommended for persons who are presumed infected with INH-resistant M. tuberculosis. Preferred treatment for pregnant women (with pyridoxine/vitamin B6 supplements)

*Use Directly Observed Therapy (DOT) or Self-Administered Therapy (parentally-administered SAT to children)

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Risk factor for TB

Risk for TB infection

- Closes contact
- Foreign born
- HCW, congregate setting

Risk for TB progression

- Recent infection/TST converters in 1st 2 years after
- Age
- HIV+
- Immunosuppression
  - Including TNF-α antagonists
- PMH of untreated TB or fibrotic lesions on X-ray
- IVDA, ETOH, Tobacco
- Medical conditions
- Medically underserved

Silicosis, DM, ESRD, transplants, CA of head and neck, gastrectomy jejunoileal bypass, Low body weight (> 10% below ideal)

Case 1

- 43 yo female is referred to your TB clinic after a recent pre-employment evaluation . She was found to have a positive interferon gamma release assay. The patient is originally from Thailand and has been in Arizona for 5 years. The patient denies weight loss, fever, night sweats. Pt has dry nonproductive cough x 4 weeks.
- What is the best next step?

  A. Masking the patient

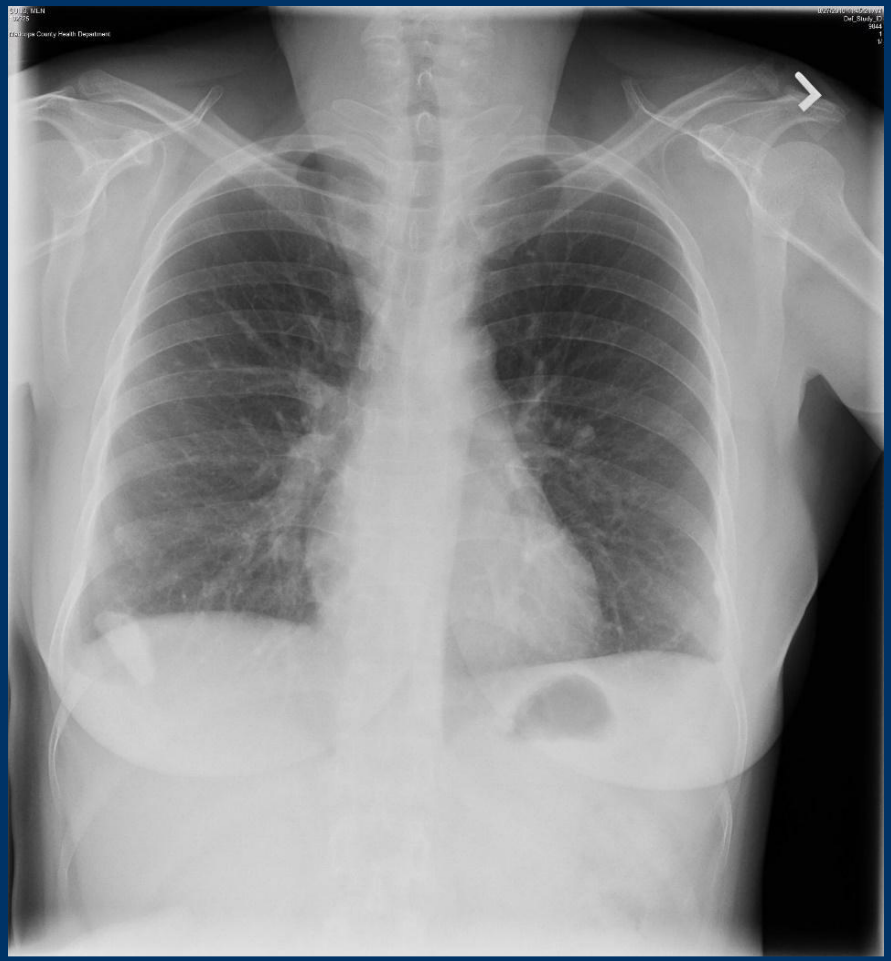
  B. Initiate treatment for latent infection

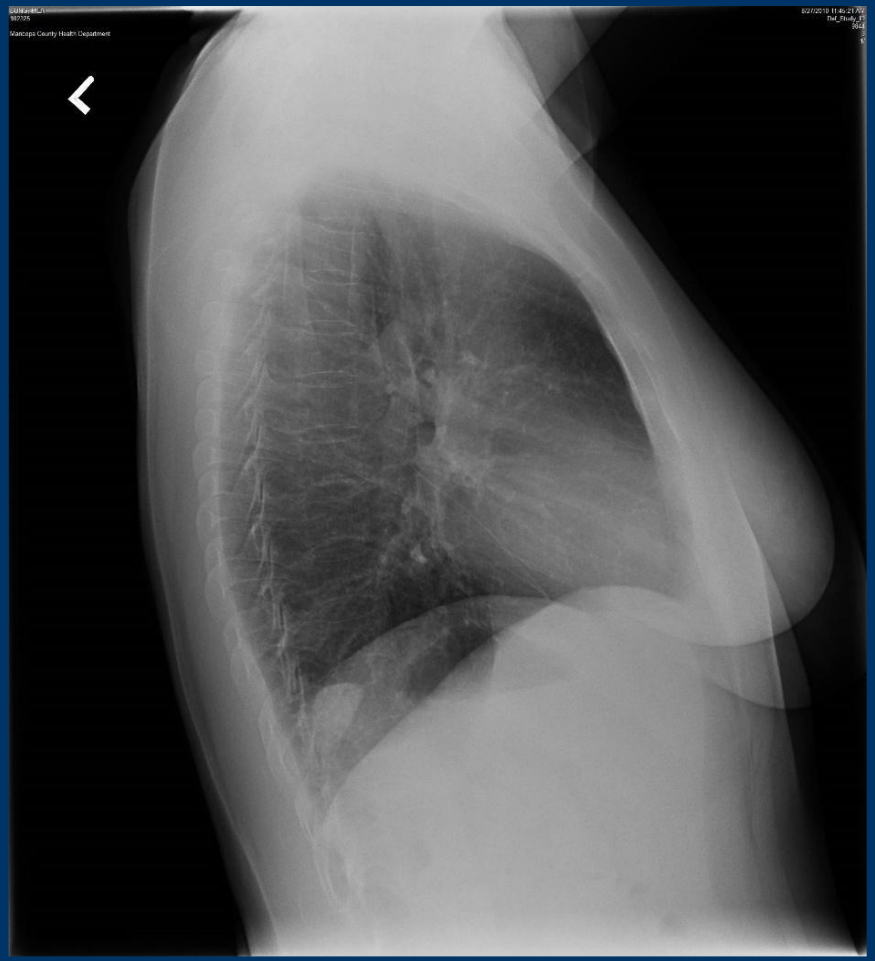
  C. Obtain cocci serologies

  D. No further workup for TB is needed

  E. Obtain a chest radiograph

Case 1





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Case 1 continued…

- Based on your interpretation of the radiographs which of the following would be the most appropriate next step?

A. Mask the patient

B. Initiate treatment for latent TB

C. Obtain cocci serologies

D. Initiate treatment for active TB

E. Collect sputum samples for AFB

Case 1 Continued…

- You have decided that the patient should be treated for latent TB infection. What regimen is preferred for this patient?

A. INH + Rifampin once weekly x 12 weeks

B. Moxifloxacin x 6 months

C. Isoniazid + Rifapentine once weekly x 12 weeks

D. INH daily x 6 months

E. INH daily x 9 months

Diagnosis

TB Disease

Diagnosis of TB Disease

- + History
- + TST / IGRA
- + Chest Radiograph
- + 3 Sputum [or Pathologic Specimen]
  - AFB staining->>>Culture
  - PCR
    - Xpert MTB/Rif
    - NAAT*

*CDC. Updated Guidelines for the Use of Nucleic Acid Amplication Test in the Diagnosis of Tuberculosis. MMWR 2009;58:7-10

Classic History

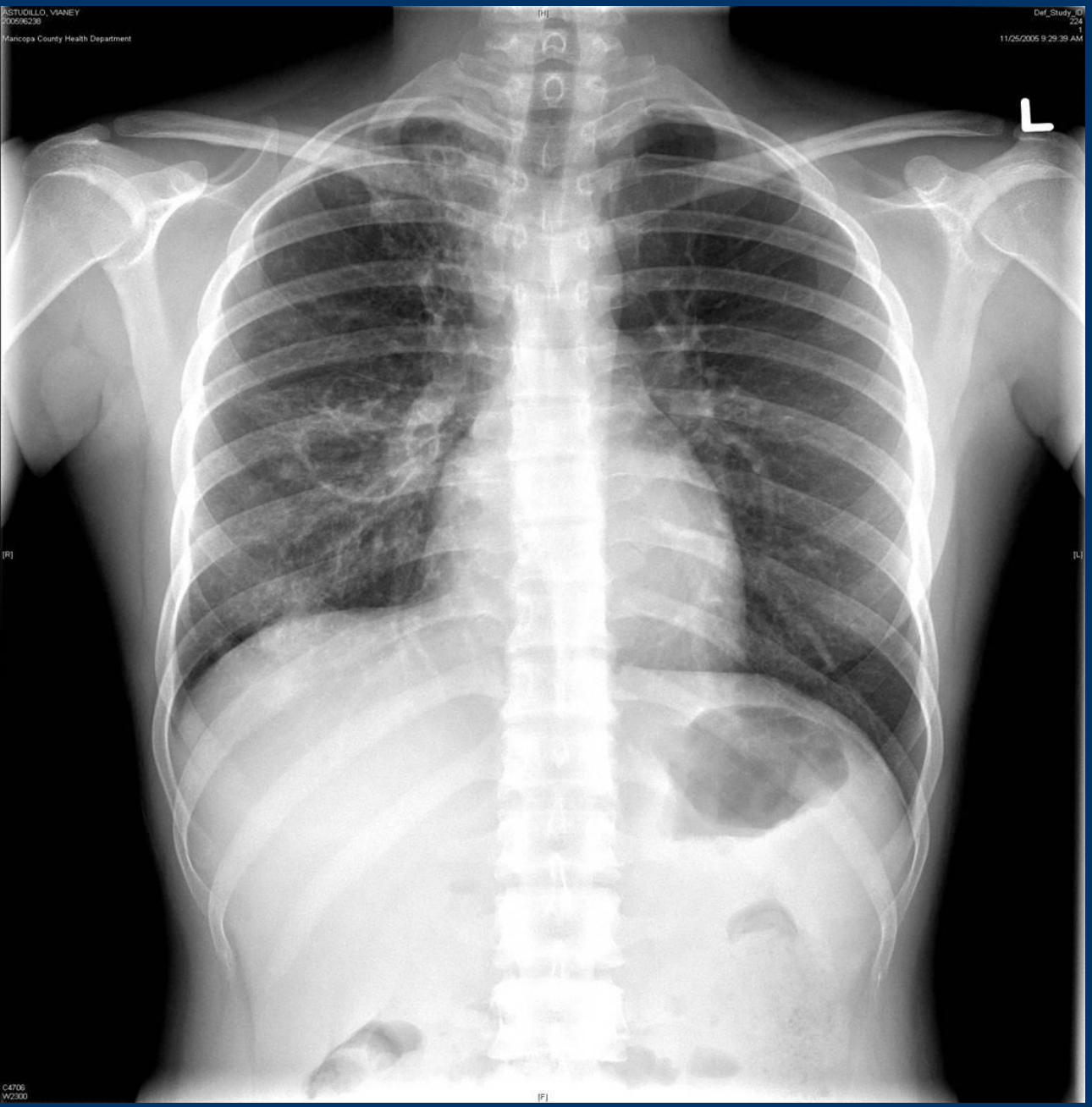
Pulmonary

- Fever, chills, night sweats, weight loss
- Chronic cough, productive
- Hemoptysis

Extrapulmonary

- Fever, chills, night sweats, weight loss
  - Lymphadenopathy
  - Bone pain
  - Pleural effusion

Adenosine deaminase
Free IFN-gamma



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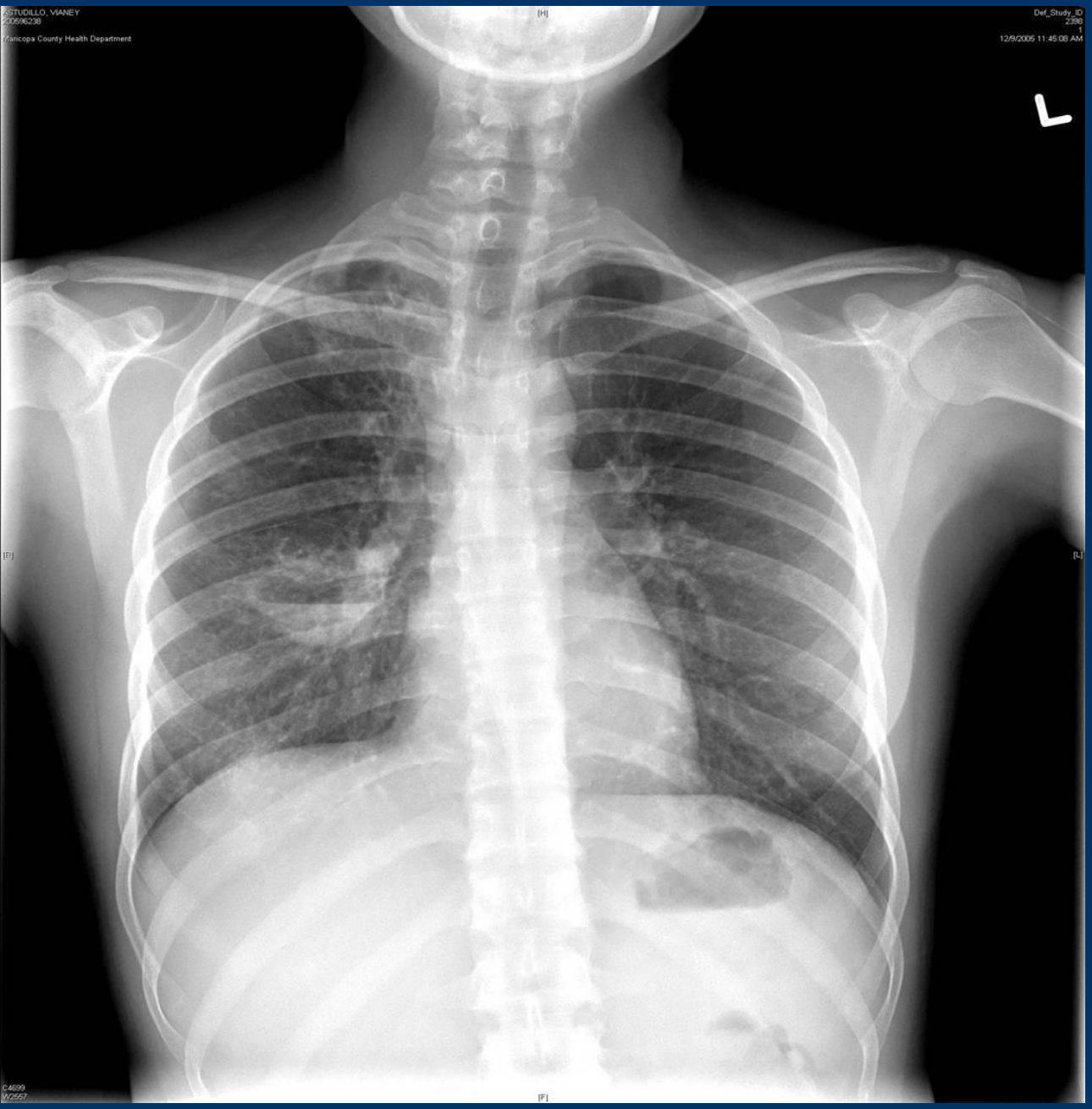

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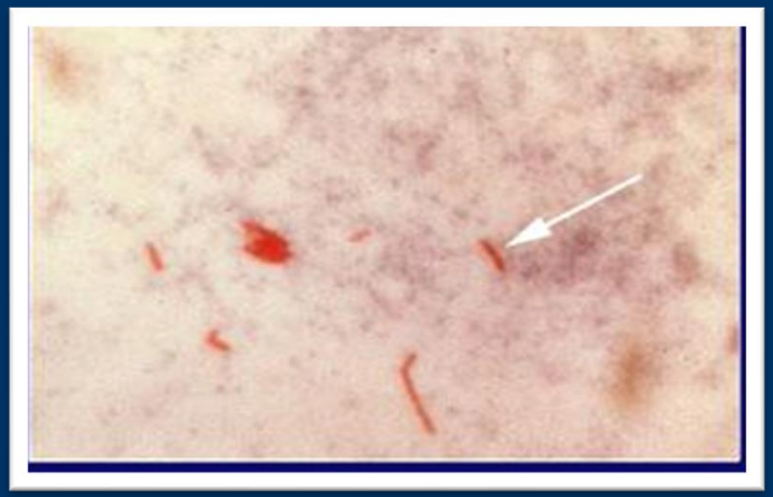
Microbiologic Test

Acid Fast Bacillus

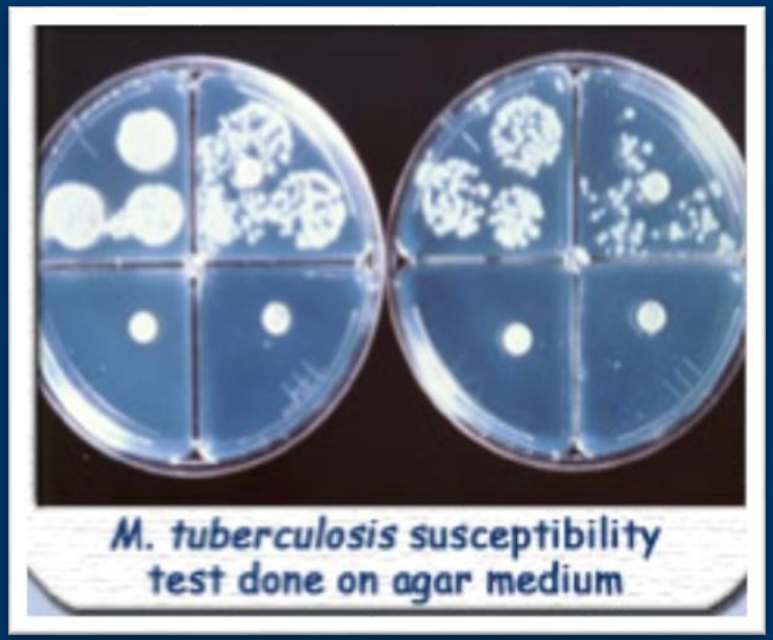
AFB Smear

- 3 Sputum specimens >5mls
- Obtained in early am Increases sensitivity
- 8 hours apart
- Induced sputum if patient can not produce expectorated specimen
- If BAL specimen, following specimens maybe induced or expectorated



AFB smear and culture

- AFB smear
  - Smear Negative
  - Smear Positive
- AFB liquid media
  More sensitive
  3-4 weeks
- AFB solid media
  Culture final results available at
  6-8 weeks
  - + MTB
  - + NTM or MOTT
  - Negative



CULTURE IS THE GOLD STANDARD

Molecular Test*

Category	Use	Examples
Automated, non-integrated NAAT	*M. tuberculosis* detection	Amplified *M. tuberculosis* Direct test (Gen-Probe); Amplicor *M. tuberculosis* (Roche) LCx (Abbott) DTB (Becton Dickson Biosci.
Line probe manual NAAT and hybridization	*M. tuberculosis* detection and drug sensitivity test for INH and RIF	Anyplex™ MDR-TB Test (Seegene); **Geno**Type® **MTBDR*plus*** (Hain LifeScience); INNO-LiPA Mycobacteria (Innogenetics)
Automated, integrated NAAT Molecular beacon	*M. tuberculosis* detection and drug sensitivity test for RIF	Xpert MTB/RIF (Cepheid) sensitivity of Xpert 98% if smear (+), 67% if smear (-) Specificity was 99%
		Pyrosequencing (PSQ)

*molecular test for ID of mycobacterial species from culture not included

NOT FDA approved or available in US Not currently recommended to test in US low prevalence RIF resistance->lower PPV

Xpert MTB/RIF

When, where, how, why to isolate?

- WHEN: Suspect active TB
- WHERE / HOW: depends where: in clinic, hospital or home
  - simple surgical mask clinic or hospital
  - place in Airborne isolation rooms (negative pressure rooms) hospital
  - Or isolate at home (if no others are put at risk!)

  need to inform patient that they can not leave the home except to come to TB doctor appointments.
- WHY: so you and others don't get infected!

Infection Control

- Airborne precautions for suspected cases
  - If in doubt isolate
- Personnel respiratory protection
  - N95
  - PAPR (Purified Air Purifying Respirator)

- Surgical mask on patient
- Clearing Patient
  - 3 AFB negative smears
  - 8 hours apart
  - BAL specimen counts for one
- Alternative diagnosis

Case 2

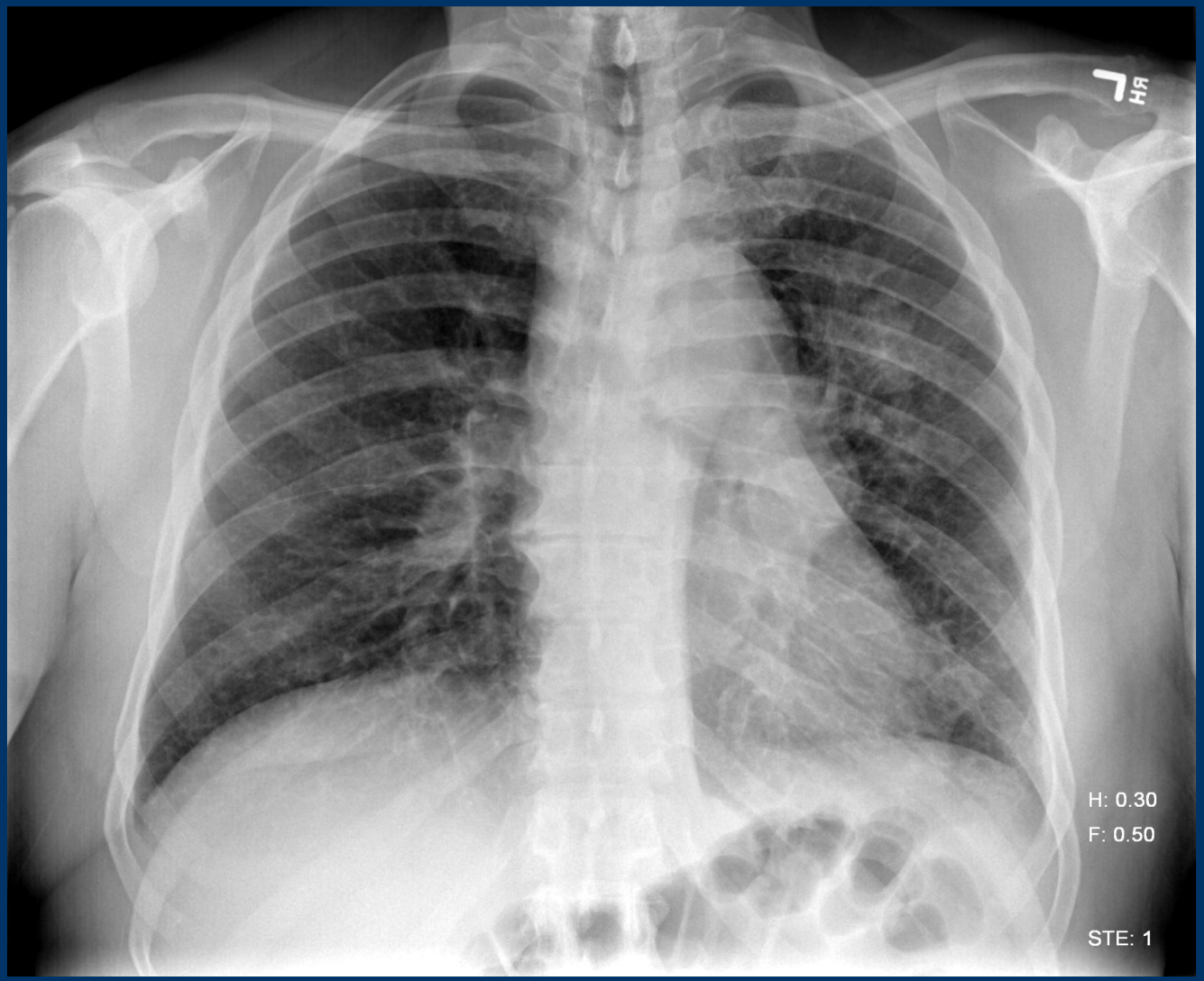
- Mr. Posadasi is a 61 yo AA gentleman who is being admitted from the ED after presenting with a 3 week h/o shortness of breath, chest pressure, fevers, chills, night sweats and weight loss. He reports one loose stool today. He seen at an outside facility where he was given treatment for CAP as well as dexamethasone. His CTA at that time was thought to be consistent with an "atypical" pneumonia.

- •VS HR 77 RR 17 BP 165/76 SaO2 97% RA

Case 2

- As the admitting resident what are your next steps?
  - Patient placement
  - History
  - Testing
    - Lab
    - Imaging
  - Treatment
    - Antimicrobial coverage
    - Timing (STAT, today?...)

Case 2



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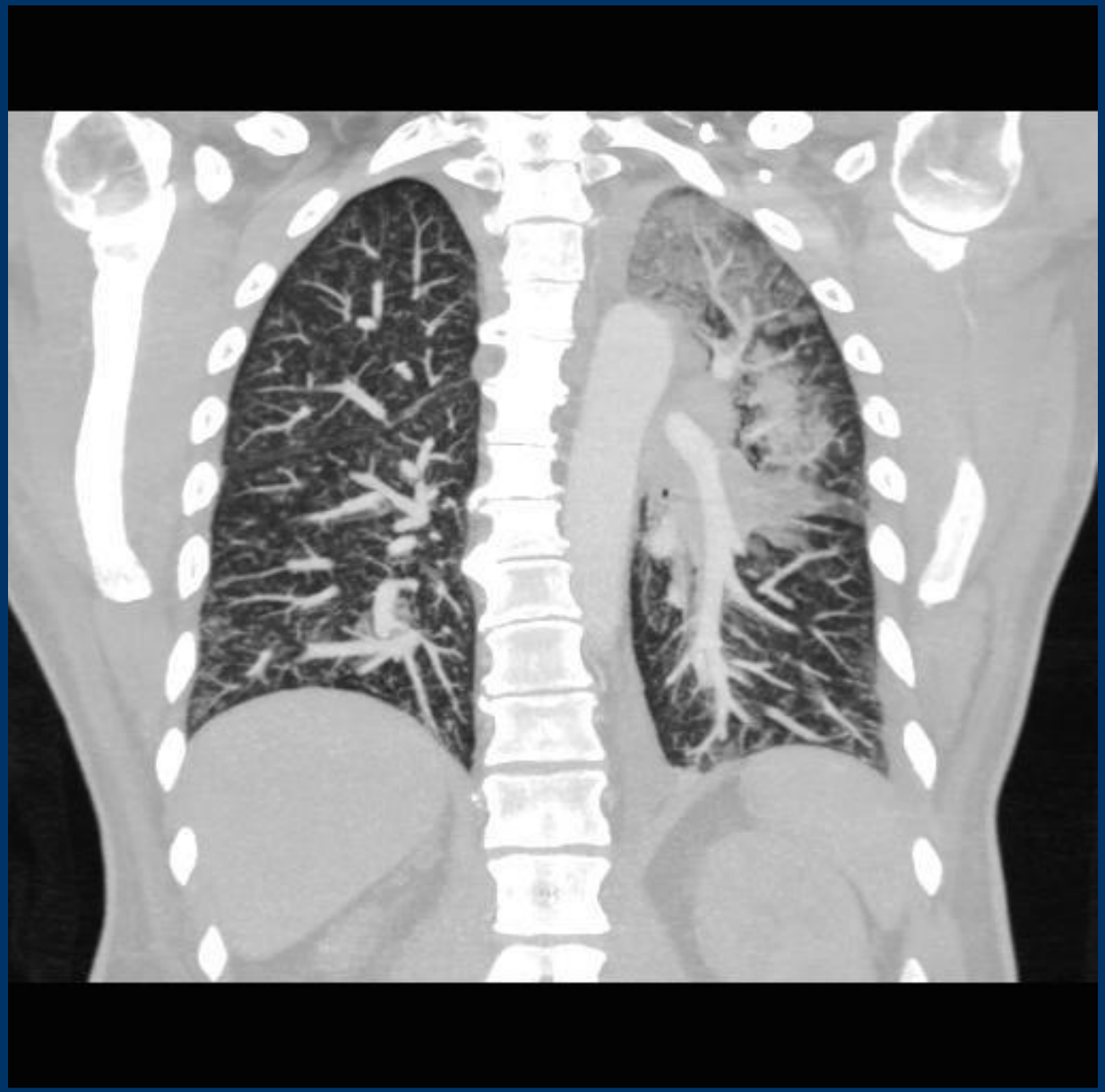
Case 2



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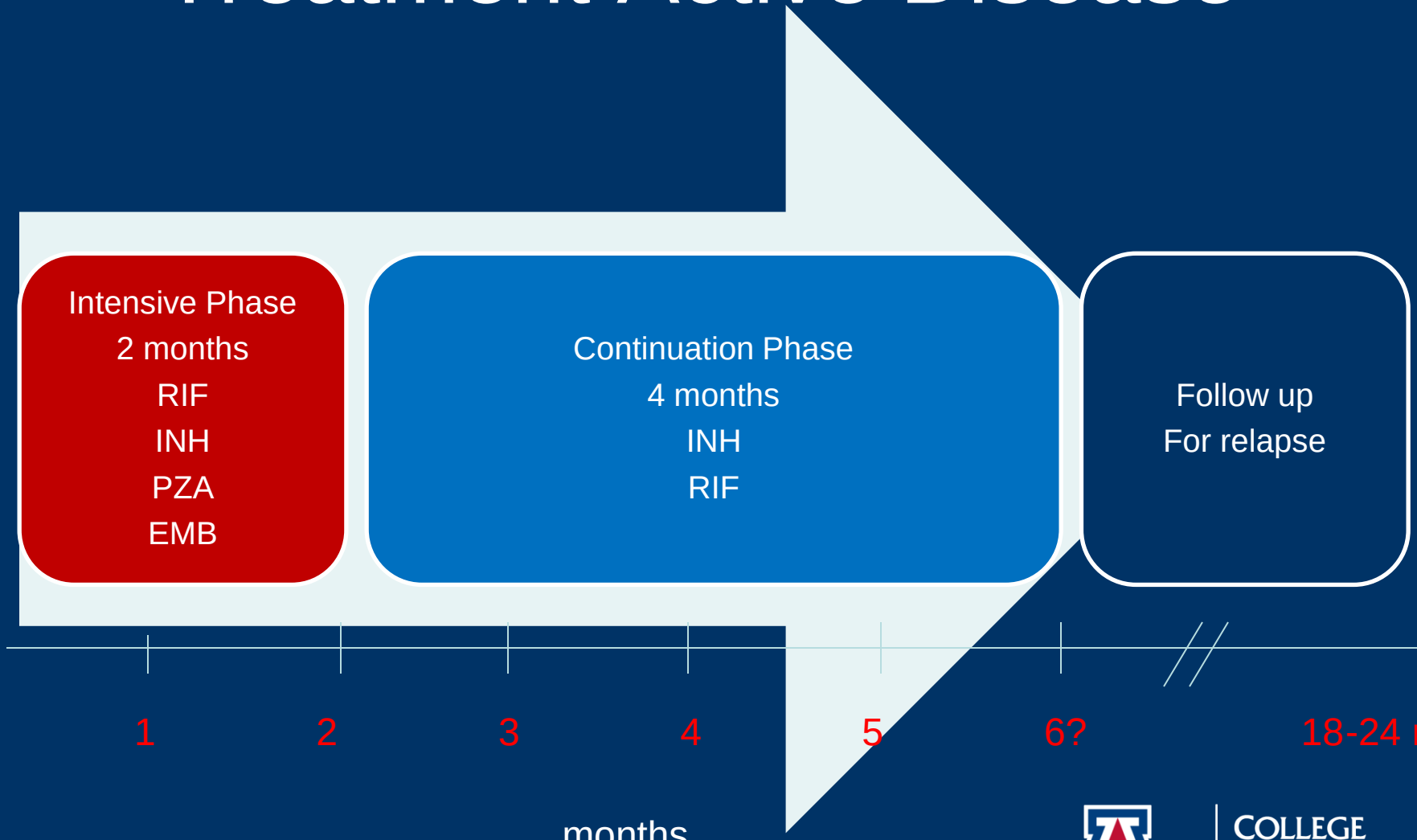
Treatment

Treatment Active Disease



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Resistance

Mutation/bacteria/cell division

- Mutation rates of M tb
  - Rifampin 3.32×10^{9}
  - Isoniazid 2.56×10^{8}
  - Pyrazinamide $1 \times 10^{?}$
  - Ethambutol 1×10^{7}

Resistance

Mutation/bacteria/cell division

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  - ~~Isoniazid 2.56×10^{8}~~
  - Pyrazinamide $1 \times 10^{?}$
  - Ethambutol 1×10^{7}

Adverse Drug Reactions (ADR)

Serious Adverse Effects

- Hepatic Toxicity
  - INH and neurotoxicity (to prevent Rx B6 pyridoxine)
  - Rifampin
    - ^cytochrome p450
    - Red orange discoloration
  - Pyrazinamide
- Optic Neuritis
  - Ethambutol
- Streptomycin
  - Renal, Otic, do not use in pregnancy->deafness in the child

Resistance

The likelihood of mutation then depends on the number of organism

The larger the population of bugs the more likely a mutation occurring

More bugs = More drugs

$P = 1 – (1-r)^n$

P is the Probability of drug resistance emerging
where r is the mutation rate;
n is the number of organism, in an adult estimated to be 10^8

Treatment Problems

- Adherence to therapy
  - 30 - 50% of patients will be significantly nonadherent
  - physicians cannot predict

Drug Resistance

- Multidrug resistant TB (MDR)
  - Resistance to INH and Rifampin

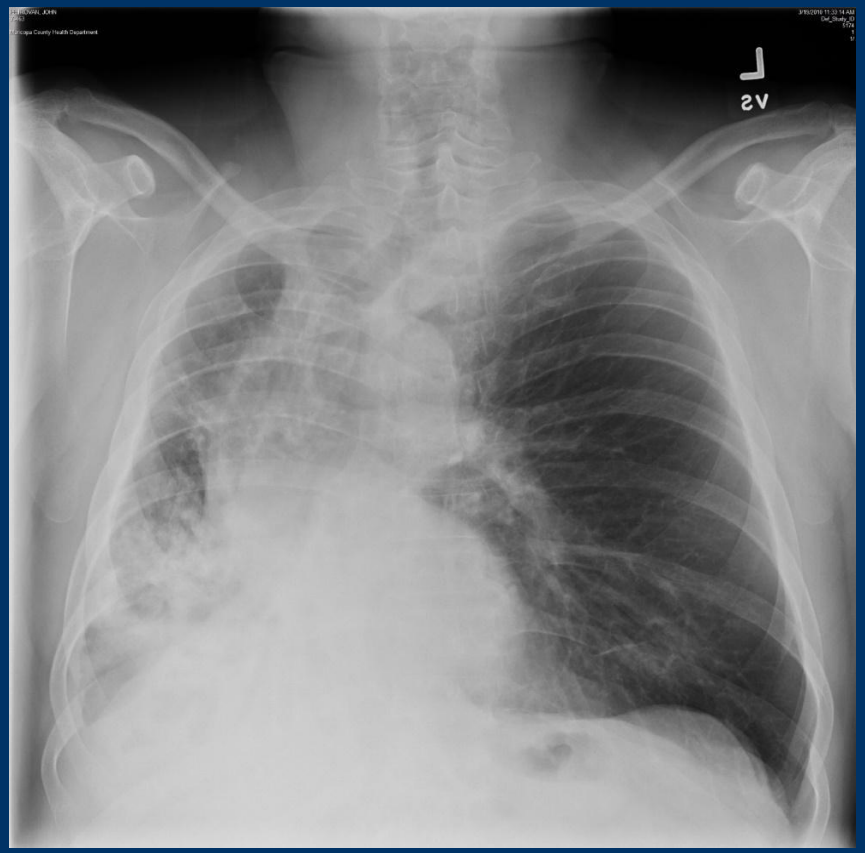
- Extensively Drug Resistant (XDR)
  - MDR-TB plus resistance to any
    - fluoroquinolone
    - and at least 1 of 3 injectable 2nd line drugs (amikacin, capreomycin, kanamycin)

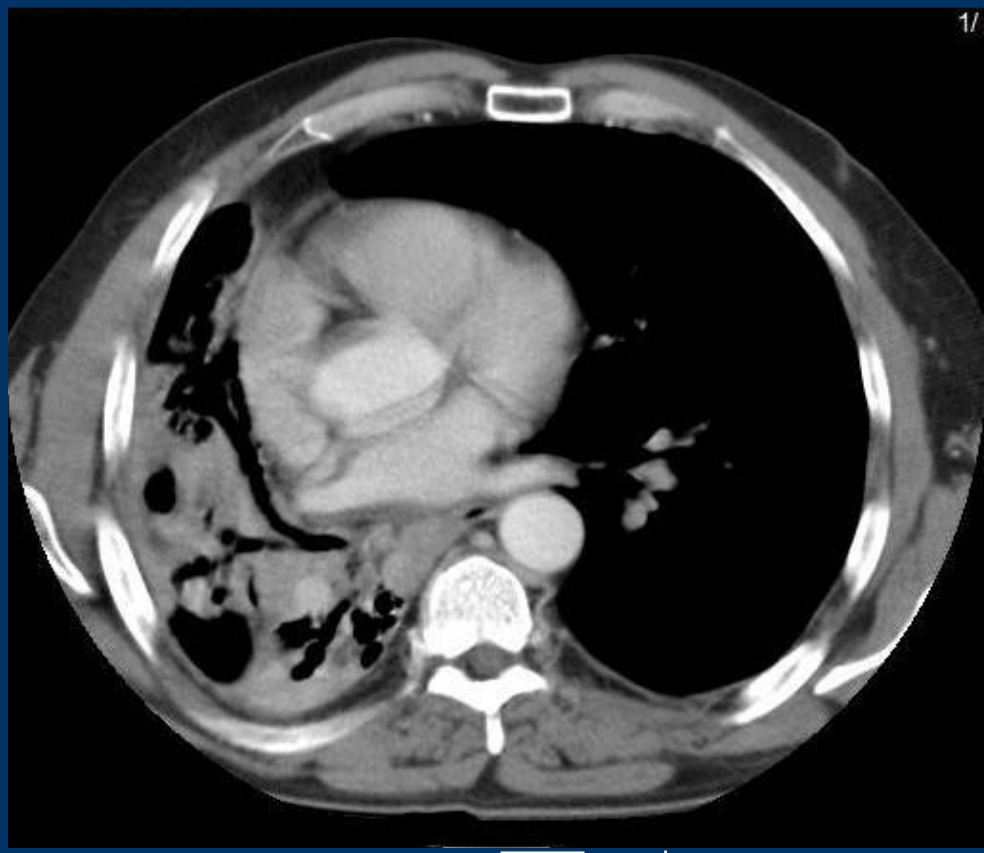
Case 3

- 60 yo male was referred for admission as a suspect case of active TB disease. He is HIV negative. The referring facility reports that he has a positive TST of 18 mm. A Quantiferon® was also done and found to be positive. Pt reports 20 lbs weight loss in the last 8 weeks, productive cough and night sweats.
- Of the following which are the appropriate test to request?
  - A. Cocci serologies
  - B. Hemoglobin A1C
  - C. Procalcitonin
  - D. CMP
  - E. Sputum for AFB smears

Case 3 continued…

Upon arrival , films obtained





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Case 3 continued…

- From an infection prevention point of view, which are an appropriate intervention when the patient arrives?

- A. Place patient in contact isolation
- B. Place a N95 respirator on patient
- C. Place patient in negative pressure room
- D. Srtaff entering room wear PAPR or N95

Case 3 continued…

- AFB smear : 4+
- Xpert MTB/Rif: + MTB with Rif resistance NOT detected
- What is the significance of the XpertMTB/Rif results?
- When is TB therapy indicated?

A. Now

B. Wait for full susceptibilities

C. Wait to see if it grows in culture. PCR detection does not indicate viable organism

Case 3 continued….

- What is the most appropriate regimen to initiate for treatment?

- A. Isoniazid + Rifampin
- B. Isoniazid + Rifampin + Pyrazinamide+ Ethambutol + B3
- C. Isoniazid + Rifampin +Moxifloxin
- D. Moxiflocin + Linezolid+ Bedaquiline+cycloserine

Case 3 continued

- Based on the available information what is the most reasonable duration of treatment?
    - A. 6 month
    - B. 9 months
    - C. 12 months
    - D. 18 months

Questions?

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