TUBERCULOSIS

- Pathogenesis and Transmission

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- Pathogenesis and Transmission
- Infection to Disease
- Diagnostic & Isolation Updates
- Treatment Updates

Pathogenesis

- Droplet nuclei of 5μm or less are generated by individuals with TB and these contain 1-10 bacilli
- A single bacillus can cause disease, but 5-200 are needed to cause human infection
- Once inhaled, the bacilli become lodged in distal sub-pleural foci usually in the lower lobes

Pathogenesis

- Once deposited in the alveolar space, the bacilli are ingested by non-activated alveolar macrophages
- The bacilli are either destroyed here or multiply
- The logarithmic multiplication of bacilli is followed by cell-mediated immunity in 3-4 weeks

Pathogenesis

- During the first several weeks after infection, tubercle bacilli hematogenously spread gaining access through pulmonary lymphatics
- Spread is preferential to areas of high oxygen tension
- Usually the primary focus is eradicated within weeks or months but if progression continues – progressive primary disease

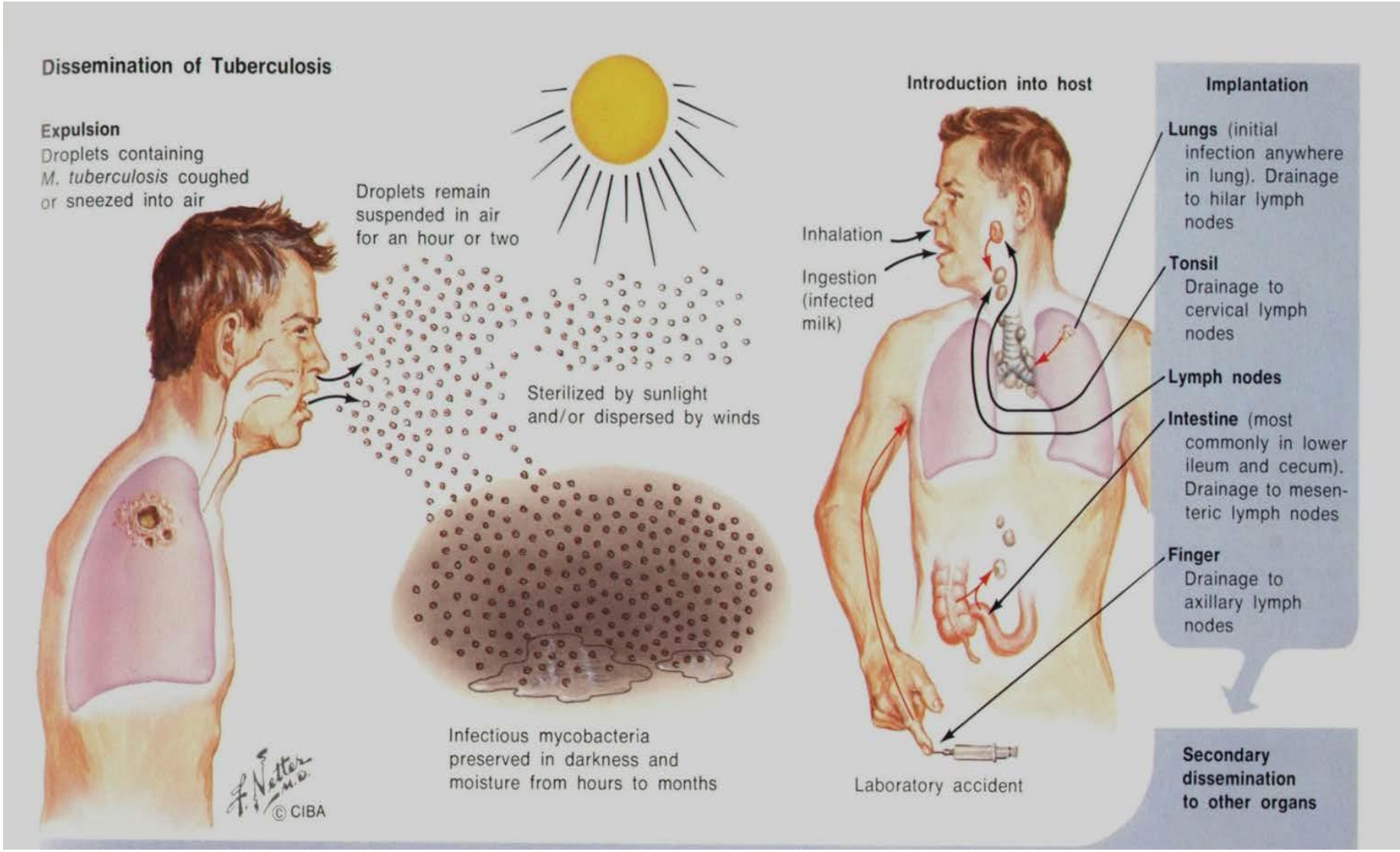
Pathogenesis

- Exposure to a person with active TB results in infection in about one third of those without HIV
- Of those infected, 3-5% develop TB within one year *and an additional 3-5% develop TB at some point thereafter*

Transmission

- Calculated that there was one infectious dose in 11,000 to 12,500 cubic feet of air
- Infectivity of patients was very heterogeneous with eight out of 130 patients accounting for almost half of all infections.
- Untreated patients with drug-susceptible TB were much more infectious.
- Drug susceptible disease is four to eight times more infectious than resistant disease.
- UV light is very effective in preventing infection.

Transmission of Tuberculosis



Transmission

Factors related to transmission are going to be related to either

Characteristics of the index patient

OR

Characteristics of contacts

Index Patient Characteristics

- Extent of disease
- Duration that source case and the contact are together and this includes proximity
- Local air circulation
- Other factors that may be important but have not been substantiated include, infective burden of MTB, previous exposure and infection, virulence, and a contact's intrinsic predisposition for infection.

Characteristics of Contacts

- The most important characteristics determining disease progression once infected are age and immune status.
- Younger children are more likely to progress to active disease and are more likely to have short latent periods followed by potentially lethal forms of the disease.
- Therefore children under five are high priority for therapy after exposure to a case.

Immune Status

- HIV's effects are well-known with rates of progression to active disease after infection of 35-162 per 1,000 person years.
- Other forms of immune suppression are important with progression including steroid therapy with prednisone equivalent of > 15mg per day for > 4 weeks, organ transplantation anti-rejection drugs, cancer therapy, and TNF-α antagonists.
- Other medical conditions have a lesser effect on progression after exposure.

Exposure and Transmission

- In an enclosed space the volume of air, the circulation, and the exhaust rate of the air are important predictors of transmission.
- The commonly used terms of “close” and “casual” are not defined and should be avoided.
- New contact guidelines recommend using size as a way to grade exposure settings.

Likelihood of Infection

- Dependent on intensity, frequency, and duration of exposure
- Examples include:
  - Airline passengers seated for eight hours or more in the same or adjoining row as a person who is contagious are more likely to be infected than others.
  - One set of criteria includes a monthly hourly total for exposure to non-cavitary cases before infection occurs (120 hours total).

Tuberculosis Infection – No Disease

- Can not spread to others
- Not considered a TB case
- Positive skin test reaction
- X-ray negative
- No symptoms
- Potential for active disease

Progression from Infection to Disease is Increased by . . .

- HIV infection
- X-ray evidence of old, untreated TB
- Substance abuse, injecting drug use
- Silicosis, diabetes
- Certain therapies
- Certain cancers
- Underweight by 10% or more

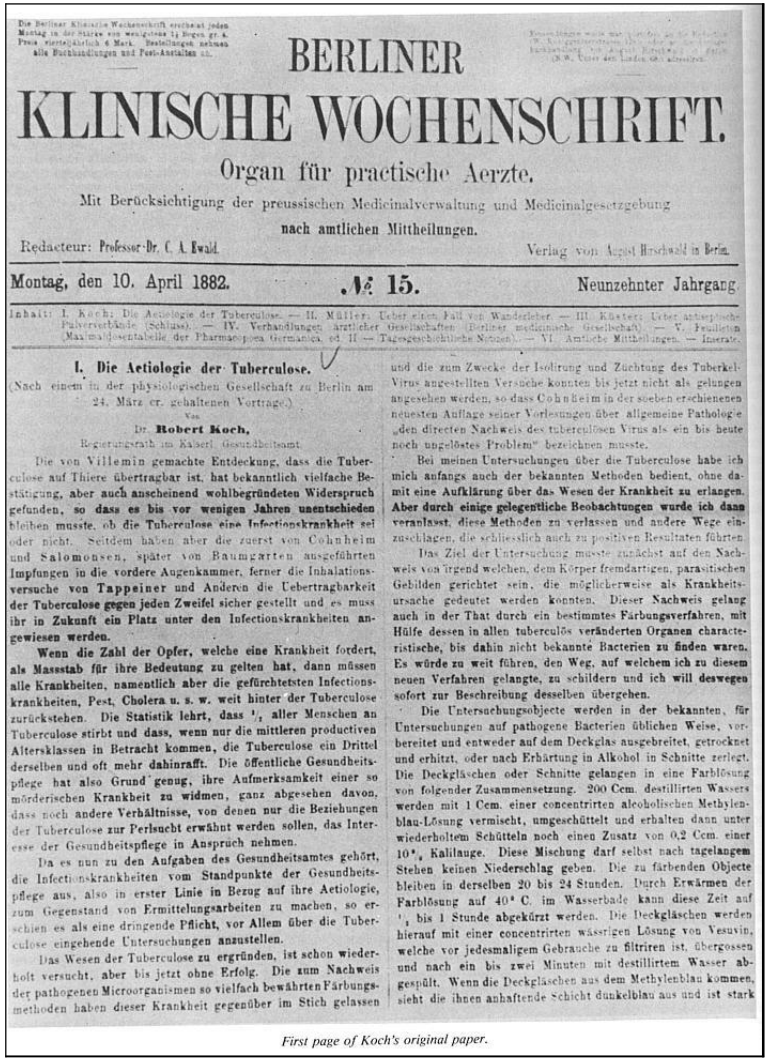
Disease Progression

- Progression from infection to disease caused by an inability to contain infection
- 5-10% of all HIV(-) will progress from infection to disease
- Up to 8% per year of TST(+), HIV(+) patients will progress from infection to disease
- The average patient with active TB infects 30 other individuals

Transmission and Pathogenesis of TB

- Tuberculosis is spread by airborne droplets (“droplet nuclei”)
- Most persons exposed to a person with tuberculosis do not become infected
- Close contacts are at high risk of acquiring infection
- Ten percent of infected persons will develop clinical tuberculosis
- Persons with tuberculosis infection but no disease are not contagious
- Cavitary or smear positive patients are more infectious than noncavitary or smear negative patients

Diagnosis of Active TB Disease



BERLINER

KLINISCHE WOCHENSCHRIFT.

Organ für practische Aerzte.

Mit Berücksichtigung der preussischen Medicinalverwaltung und Medicinalgesetzgebung

nach amtlichen Mittheilungen.

Redacteur: Professor Dr. C. A. Ewald. Verlag von August Hirschwald in Berlin.

Montag, den 10. April 1882. № 15. Neunzehnter Jahrgang.

Inhalt: I. Koch: Die Aetiologie der Tuberculose. — II. Müller: Ueber einen Fall von Wanderleber. — III. Küstner: Ueber antiseptische Pulververbände (Schluss). — IV. Verhandlungen ärztlicher Gesellschaften (Berliner medicinische Gesellschaft). — V. Feuilleton (Maximaldosentabelle der Pharmacopoea Germanica, ed. II. — Tagesgeschichtliche Notizen). — VI. Amtliche Mittheilungen. — Inserate.

I. Die Aetiologie der Tuberculose.

(Nach einem in der physiologischen Gesellschaft zu Berlin am 24. März cr. gehaltenen Vortrage.)

Von

Dr. **Robert Koch,**

Regierungsrath im Kaiserl. Gesundheitsamt.

Die von Villemin gemachte Entdeckung, dass die Tuberculose auf Thiere übertragbar ist, hat bekanntlich vielfache Bestätigung, aber auch anscheinend wohlbegründeten Widerspruch gefunden, so dass es bis vor wenigen Jahren unentschieden bleiben musste, ob die Tuberculose eine Infectionskrankheit sei oder nicht. Seitdem haben aber die zuerst von Cohnheim und Salomonsen, später von Baumgarten ausgeführten Impfungen in die vordere Augenkammer, ferner die Inhalationsversuche von Tappeiner und Anderen die Uebertragbarkeit der Tuberculose gegen jeden Zweifel sicher gestellt und es muss ihr in Zukunft ein Platz unter den Infectionskrankheiten angewiesen werden.

Wenn die Zahl der Opfer, welche eine Krankheit fordert, als Massstab für ihre Bedeutung zu gelten hat, dann müssen alle Krankheiten, namentlich aber die gefürchtetsten Infectionskrankheiten, Pest, Cholera u. s. w. weit hinter der Tuberculose zurückstehen. Die Statistik lehrt, dass $^1/_7$ aller Menschen an Tuberculose stirbt und dass, wenn nur die mittleren productiven Altersklassen in Betracht kommen, die Tuberculose ein Drittel derselben und oft mehr dahinrafft. Die öffentliche Gesundheitspflege hat also Grund genug, ihre Aufmerksamkeit einer so mörderischen Krankheit zu widmen, ganz abgesehen davon, dass noch andere Verhältnisse, von denen nur die Beziehungen der Tuberculose zur Perlsucht erwähnt werden sollen, das Interesse der Gesundheitspflege in Anspruch nehmen.

Da es nun zu den Aufgaben des Gesundheitsamtes gehört, die Infectionskrankheiten vom Standpunkte der Gesundheitspflege aus, also in erster Linie in Bezug auf ihre Aetiologie, zum Gegenstand von Ermittelungsarbeiten zu machen, so erschien es als eine dringende Pflicht, vor Allem über die Tuberculose eingehende Untersuchungen anzustellen.

Das Wesen der Tuberculose zu ergründen, ist schon wiederholt versucht, aber bis jetzt ohne Erfolg. Die zum Nachweis der pathogenen Microorganismen so vielfach bewährten Färbungsmethoden haben dieser Krankheit gegenüber im Stich gelassen und die zum Zwecke der Isolirung und Züchtung des Tuberkel-Virus angestellten Versuche konnten bis jetzt nicht als gelungen angesehen werden, so dass Cohnheim in der soeben erschienenen neuesten Auflage seiner Vorlesungen über allgemeine Pathologie „den directen Nachweis des tuberculösen Virus als ein bis heute noch ungelöstes Problem" bezeichnen musste.

Bei meinen Untersuchungen über die Tuberculose habe ich mich anfangs auch der bekannten Methoden bedient, ohne damit eine Aufklärung über das Wesen der Krankheit zu erlangen. Aber durch einige gelegentliche Beobachtungen wurde ich dann veranlasst, diese Methoden zu verlassen und andere Wege einzuschlagen, die schliesslich auch zu positiven Resultaten führten.

Das Ziel der Untersuchung musste zunächst auf den Nachweis von irgend welchen, dem Körper fremdartigen, parasitischen Gebilden gerichtet sein, die möglicherweise als Krankheitsursache gedeutet werden konnten. Dieser Nachweis gelang auch in der That durch ein bestimmtes Färbungsverfahren, mit Hülfe dessen in allen tuberculös veränderten Organen characteristische, bis dahin nicht bekannte Bacterien zu finden waren. Es würde zu weit führen, den Weg, auf welchem ich zu diesem neuen Verfahren gelangte, zu schildern und ich will deswegen sofort zur Beschreibung desselben übergehen.

Die Untersuchungsobjecte werden in der bekannten, für Untersuchungen auf pathogene Bacterien üblichen Weise, vorbereitet und entweder auf dem Deckglas ausgebreitet, getrocknet und erhitzt, oder nach Erhärtung in Alkohol in Schnitte zerlegt. Die Deckgläschen oder Schnitte gelangen in eine Farblösung von folgender Zusammensetzung. 200 Ccm. destillirten Wassers werden mit 1 Ccm. einer concentrirten alcoholischen Methylenblau-Lösung vermischt, umgeschüttelt und erhalten dann unter wiederholtem Schütteln noch einen Zusatz von 0,2 Ccm. einer 10% Kalilauge. Diese Mischung darf selbst nach tagelangem Stehen keinen Niederschlag geben. Die zu färbenden Objecte bleiben in derselben 20 bis 24 Stunden. Durch Erwärmen der Farblösung auf 40° C. im Wasserbade kann diese Zeit auf $^1/_2$ bis 1 Stunde abgekürzt werden. Die Deckgläschen werden hierauf mit einer concentrirten wässrigen Lösung von Vesuvin, welche vor jedesmaligem Gebrauche zu filtriren ist, übergossen und nach ein bis zwei Minuten mit destillirtem Wasser abgespült. Wenn die Deckgläschen aus dem Methylenblau kommen, sieht die ihnen anhaftende Schicht dunkelblau aus und ist stark

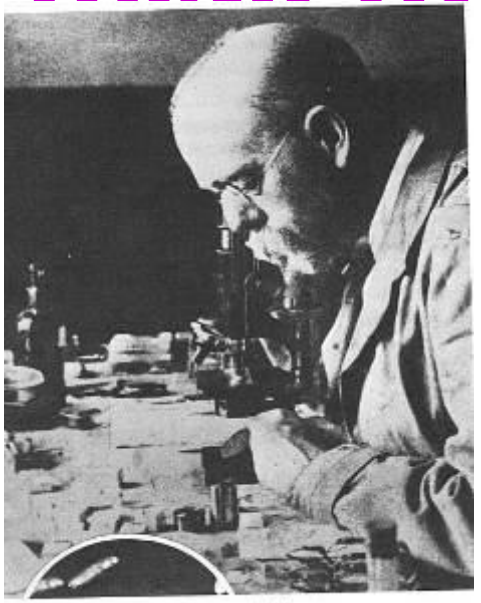
First page of Koch's original paper.

Key:

Key:

THINK TB

THINK TB



Robert Koch in his laboratory.

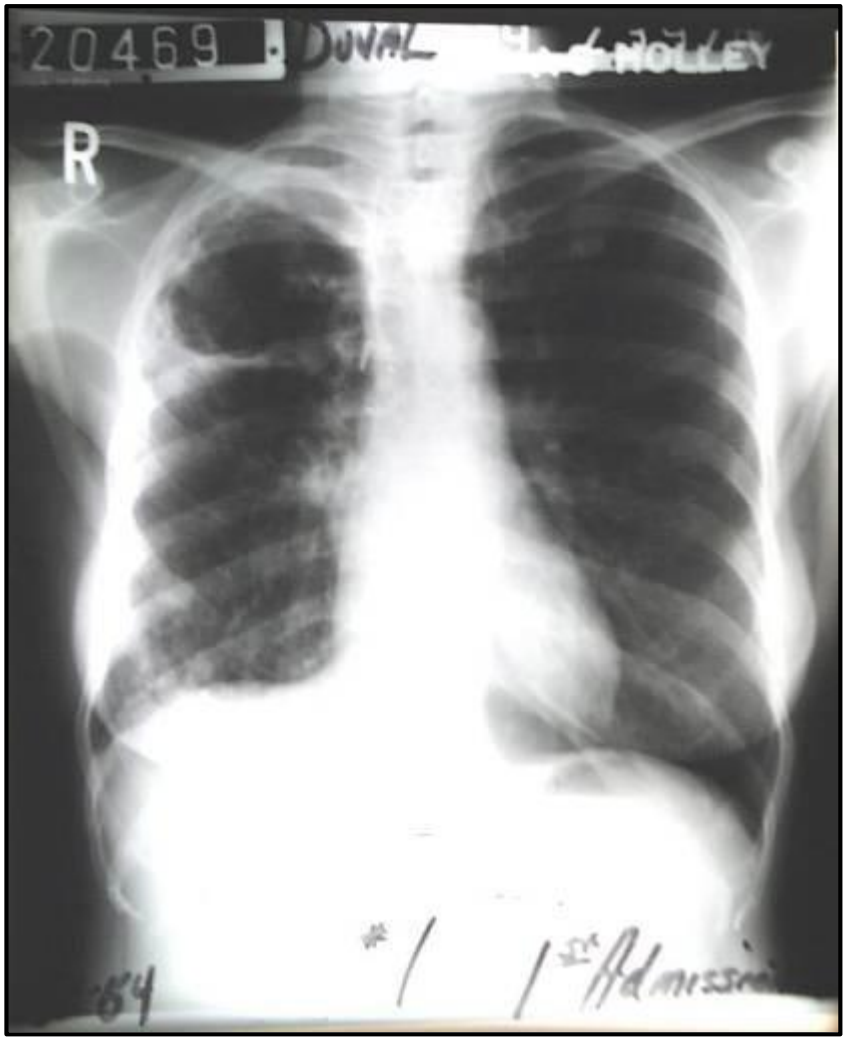
Signs and Symptoms of TB Disease

- Often of long duration
- General
  - Fatigue, malaise, weight loss, fever, night sweats
- Pulmonary
  - Prolonged cough, coughing up blood
- Extrapulmonary
  - Depends on site

CDC
SAFER·HEALTHIER·PEOPLE™

Diagnosis of TB Disease

- Chest x-ray
  - 95% of HIV(-) cases with upper lobe infiltrates and/or cavities



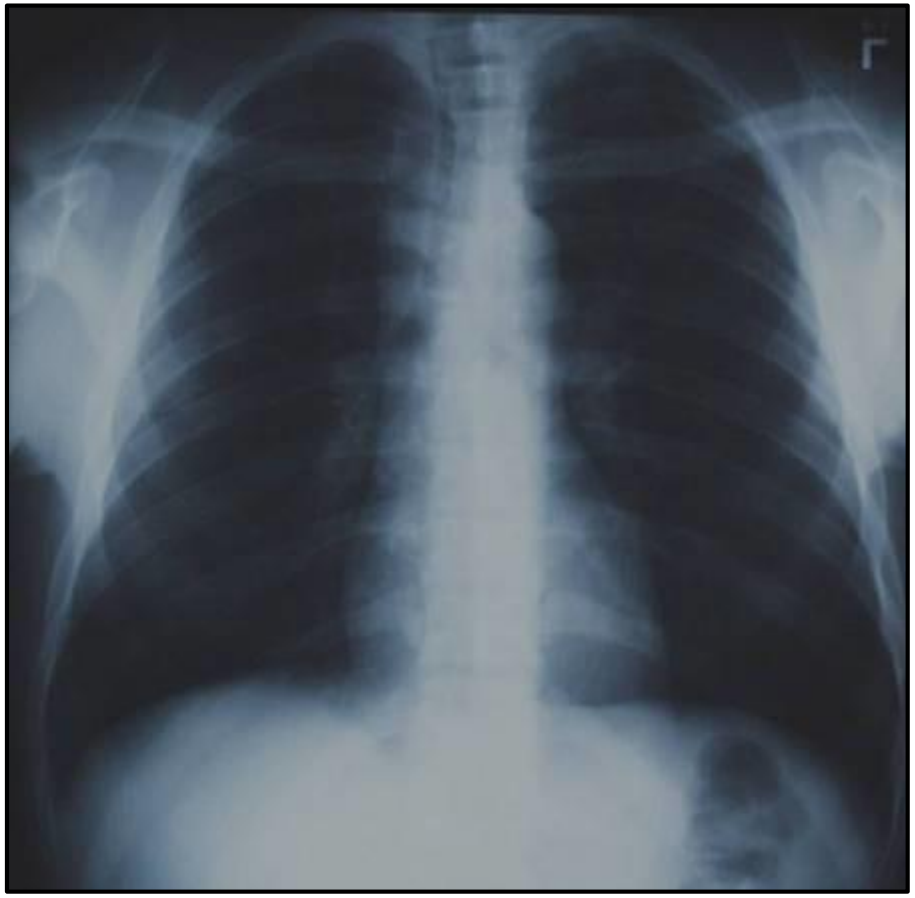
Characteristics of Chest Radiographs

- 47 patients
  - 17 with AIDS and 30 without AIDS

CHARACTERISTICS	PATIENTS WITH AIDS	PATIENTS WITHOUT AIDS	P VALUES
Hilar and/or mediastinal adenopathy	10 (59%)	1 (3%)	< 0.001
Localized pulmonary infiltrates involving middle or lower lung fields	5 (29%)	1 (3%)	< 0.05
Localized pulmonary infiltrates involving upper lobes	3 (18%)	29 (97%)	< 0.001
Pulmonary cavities	0	20 (67%)	< 0.001
No pulmonary infiltrates	6 (35%)	0	< 0.005

Diagnosis of TB Disease

- Up to 30% of HIV(+), active TB cases will have no infiltrates or cavities



Extra-pulmonary TB

- ~10% in HIV(-)
- HIV(+)
  - 33% with extrapulmonary alone
  - 33% with pulmonary alone
  - 33% both pulmonary and extrapulmonary (many with negative CXRs)
- Any organ has been noted to be involved
  - Pleural dx most common
  - Lymph nodes
  - GU
  - Bone (Need to prolong therapy)
  - Abdominal
  - CNS (Need to prolong therapy)

TB Disease Diagnosis

- Smear
  - Cheap & rapid
  - Only 40-60% positive in cases of active TB
  - The Standard for Diagnosis of TB in most of the world

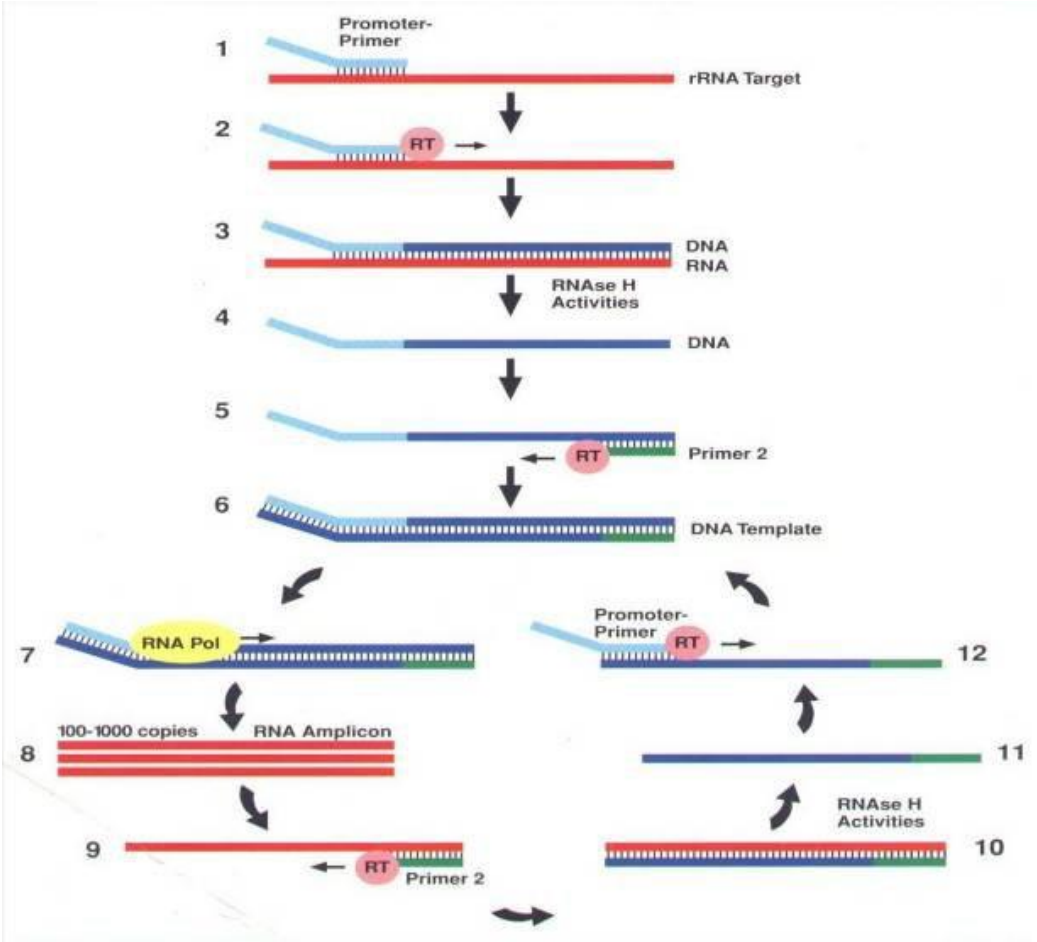
TB Diagnosis

- Culture
  - Takes 6-8 weeks by conventional
  - Takes 1-3 weeks by liquid media
  - Need ~100 organisms/ml to get 1 colony
  - Sensitivity-Positive in 80% of CDC Verified Cases
  - Specificity- 1-2% False Positive
- Susceptibility
  - Takes 1-2 weeks after positive culture
  - Molecular Techniques have the ability to give more rapid results

Most of the world does not have access to these critical laboratory tests!!!

TB Diagnosis
Nucleic Acid Amplification

- Results within eight hours 99% specificity on smear (+) cases
- Up to 80% sensitivity on three samples
- $30 to $50 per test
- Approved by the FDA for smear-positive and – negative, untreated cases
- May have a role in non-pulmonary samples



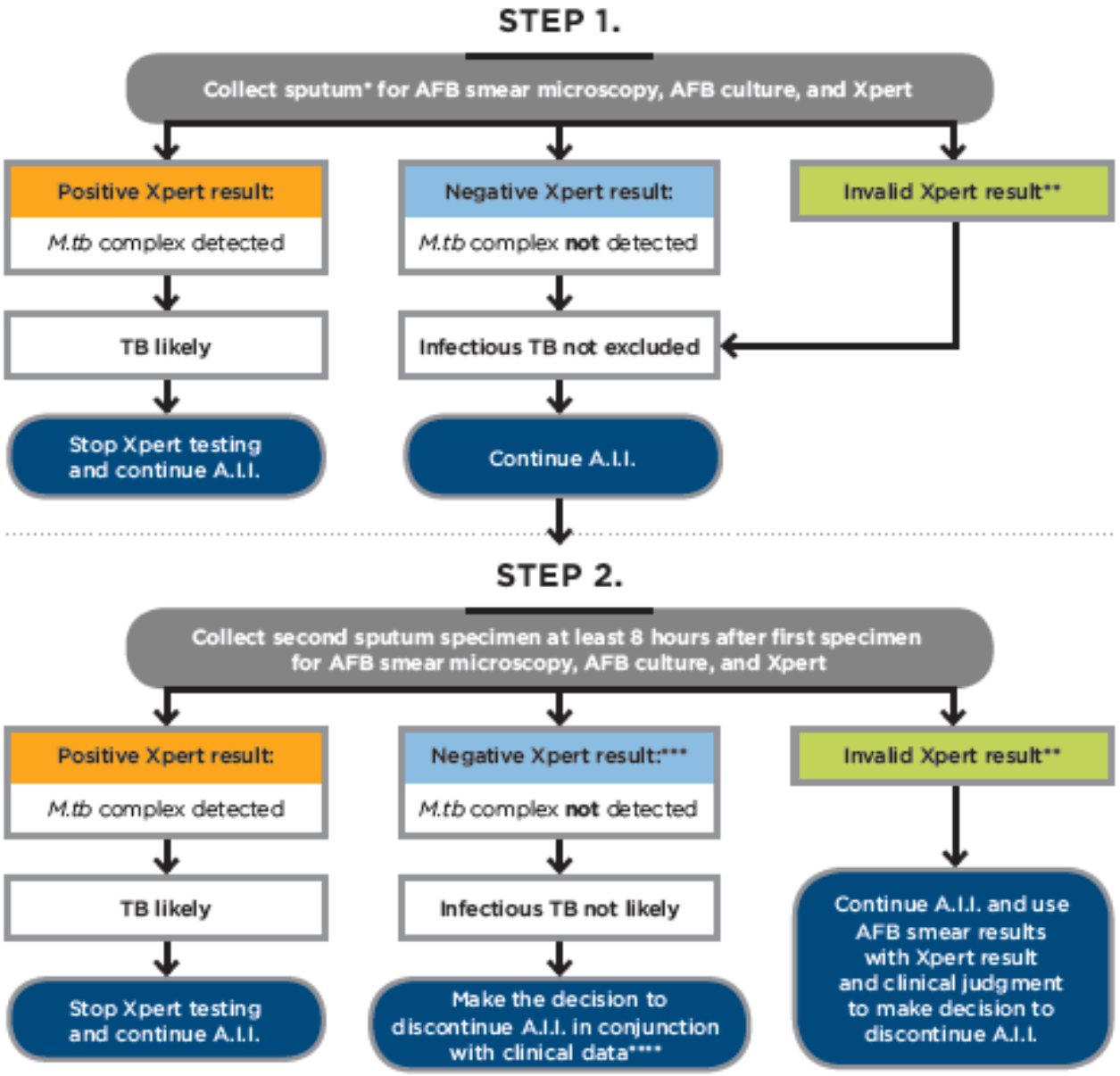
2009 NAA CDC Guidelines

"CDC recommends that NAA testing be performed on at least one respiratory specimen from each patient with signs and symptoms of pulmonary TB for whom a diagnosis of TB is being considered but has not yet been established, and for whom the test result would alter case management or TB control activities, such as contact investigations."

April 2016

The purpose of this consensus statement is to provide guidance for clinicians, nurses, and hospital infection preventionists on the use of the FDA-approved Cepheid Xpert MTB/RIF® (Xpert) Nucleic Acid Amplification (NAA) test when making decisions to discontinue airborne infection isolation (A.I.I.) for persons with suspected, infectious pulmonary tuberculosis (TB).

USE OF GENEXPERT IN DISCONTINUING AIRBORNE INFECTION ISOLATION



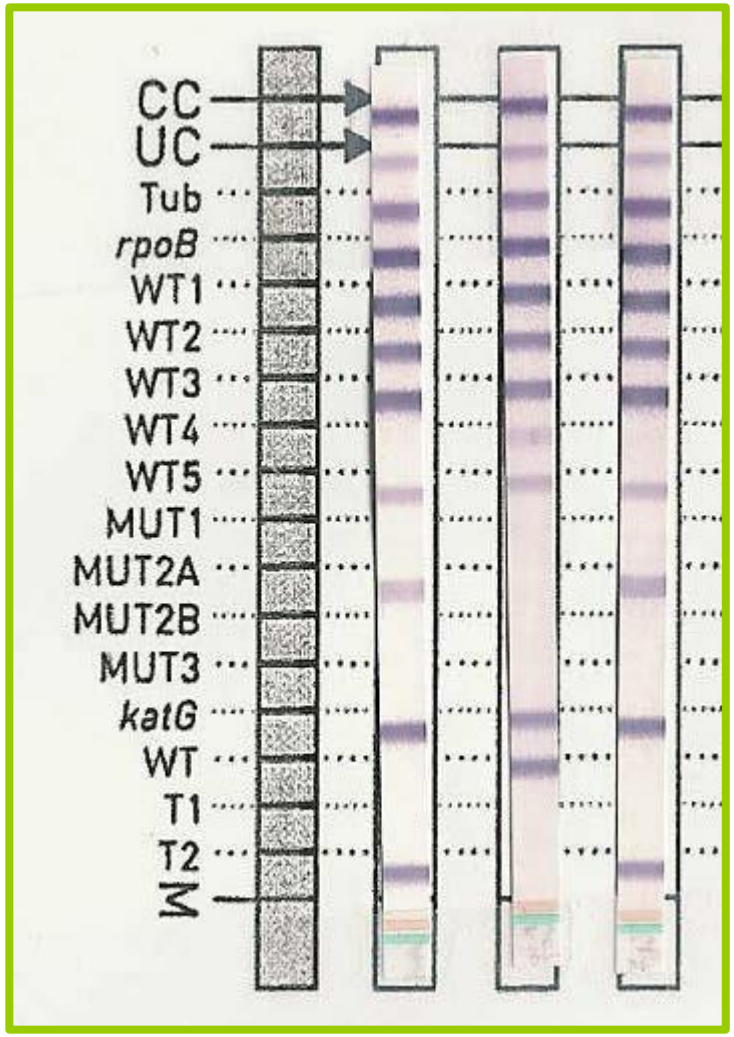
M.tb: *Mycobacterium tuberculosis* **A.I.I.:** Airborne infection isolation

Molecular testing:

Drug	Gene	% mutations
RIF	*rpoB*	>96%
INH	*katG*	40-60%
INH-ETH	*inhA*	15-43%
PZA	*pncA*	72-97%
F-quinolones	*gyrA*	75-94%
Capreomycin	*tlyA*	unknown

Curry Center: Drug-resistant tuberculosis – A survival guide for clinicians, 2nd Edition. 2008

GenoType MTB-DR (Hain Lifescience)



General Principles of Chemotherapy for TB Disease

- Existence of mutant bacilli with innate resistance to antibiotic action
- Slow or intermittent growth of mycobacterium which permits the persistence of viable organisms despite prolonged antibiotic treatment, because only actively replicating organisms are killed by antibiotics

Treatment of Active TB Disease

- Start with 4 drugs in all patients
  - INH, RIF, PZA and EMB or SM until sensitivities return
  - If pansensitive, D/C EMB or SM
  - After 2 months of therapy, D/C PZA
  - Continue INH & RIF for 4 more months for total of 6 months
- Must have culture conversion by 2 months
- 6 month regimen good for HIV(-) and (+)
- Can use BIW regimen**
  (TIW ? RIF Monoresistance in HIV pts after daily for first 2 months)
- Monitor adherence and toxicity
- DOT preferred, Combination pills for self administered

Determinants of Response to Therapy

- Clinical signs
  - Improved cough usually within two weeks
  - Fever usually within two weeks
    - However – can last four to six weeks
  - Weight gain and improved appetite
- Decreased organisms seen on smear
  - Usually markedly decreased within three to four weeks
    - However – can last for months
- Decreased counts on cultures
  - 90% convert in two months on INH/RIF/PZA

Likelihood of Infectiousness

- Probably infectious
  - Positive sputum smears with viable AFB
  - Presence or induction of coughing
  - Not treated or recently started
  - Poor clinical or bacteriologic response to prescription
- Not infectious
  - Receiving effective therapy and responding
  - Three daily negative sputums

Causes of Inadequate Response to Therapy

- **Non adherence!!!!!!!!!!!!!!!!**
  - DOT
  - Involuntary detention
- Increased drug resistance/incorrect sensitivities
- Malabsorption/increased metabolism
- Inability of drugs to penetrate effected tissues

Clinical Significance of Resistance

- If pansensitive > 95% chance of cure
- If resistant to INH > 90% chance of cure
- If resistant to rifampin > 70% chance of cure
- If resistant to INH and RIF ~ 50% chance of cure
- Before chemotherapy ~ 50% chance of cure

Assure the treatment until cure of every tuberculosis patient!

DOT therapy works!

- 95% of patients with TB will be cured by DOT
  - Decreases morbidity and mortality and cost (~ $1500/patient)
  - Decreases spread of disease
    - Average patient with TB infects 30 other individuals
  - Decreases resistance
    - MDR costs ~ $250,000 to cure with only ~ 80% success
- 5% of patients with active TB will be unable to complete therapy requiring legal interventions and facilities to cure them
    - In S.F. one non-compliant patient with MDR-TB was responsible for 40 other cases

Infection Control

- **Think TB, isolate, and start meds**
- Six to eight air exchanges/hour
- Negative pressure
- Doors closed
- All entering room wear N95 mask
- Keep in isolation until three negative smears, on medications and responding clinically

Interferon-gamma release assays (IGRAs)

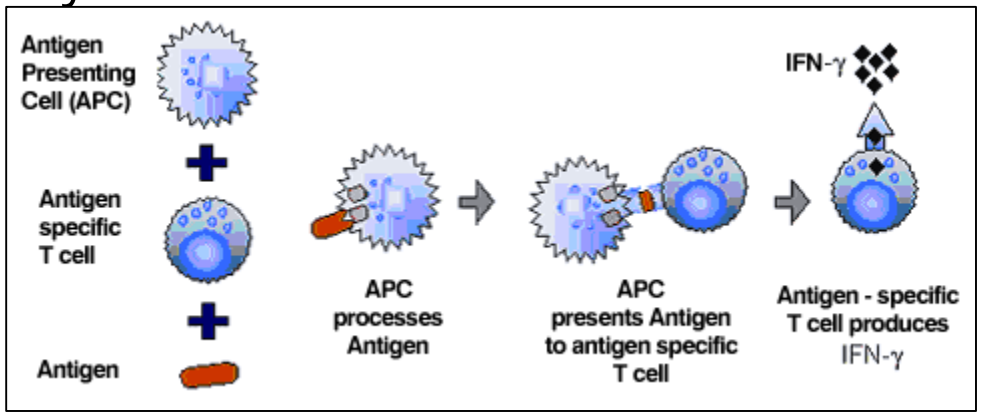
- In response to the limitations of the TST, IGRAs have been developed and have become available over the last decade
- More specific and sensitive than TST for diagnosis of LTBI
- Two IGRAs commercially available in USA
- Both IGRAs measure the secretion of the cytokine interferon-gamma (IFN-γ) by lymphocytes stimulated in vitro with TB-specific antigens

IGRA: General Points

- IGRAs are highly specific (~95%)
  - Both QFT and T-SPOT TB substantially more specific than the PPD since they contain antigens not found in BCG
  - Distinguish most NTM (except *M. Kansasii*, *M. marinum*, *M. szulgai, M. flavescens*)
  - PPD contains large number of mycobacterial proteins not specific to *M. tuberculosis*
- IGRAs have moderate to high sensitivity vs. PPD
  - QFT being as sensitive as PPD (70-80%) in immunocompetent
  - T-SPOT TB more sensitive (~90%) than QFT and PPD in immunocompromised

Whole Blood Interferon Gamma Release Assay

- IGRAs use purified antigens from MTB to stimulate peripheral-blood lymphocytes to produce gamma interferon
- QuantiFERON tests (QFT) measures gamma interferon (IFN-gamma) in the supernatant of the cell suspension
- TSPOT measures cells producing gamma interferon using ELISpot assay




thank you
danke
謝謝
ngiyabonga
teşekkür ederim
gracias
merci
obrigado
спасибо
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bedankt
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grazie
terima kasih
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