TUBERCULOSIS

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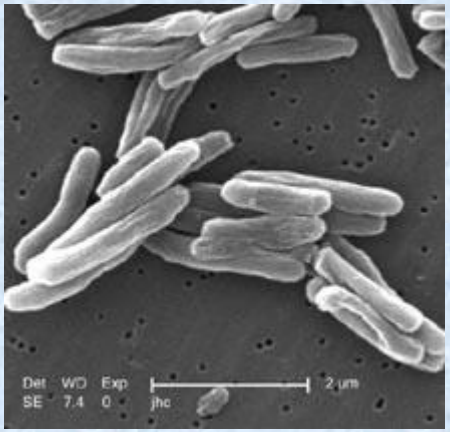
Definition

Tuberculosis is infectious disease caused by Mycobacterium tuberculosis complex

- *Mycobacterium tuberculosis*
- *Mycobacterium bovis*
- *Mycobacterium africanum*
- *Mycobacterium microti*
- *Mycobacterium canetti*
- *M. pinnipedii*
- *M. caprae,*
- *M. mungi*



Epidemiology - world 2018

- 10.4 million new cases (estimation)
- of which 1.2 million with HIV (11%)
- 1.4 million deaths from TB

  plus 0,4 million deaths from HIV with TB
- 480 000 new cases MDR-TB
  - MDR-TB treatment success rate was 52% in 2013
- 60% of new cases in 6 countries: India, China, the Russian Federation, Indonesia and Nigeria.

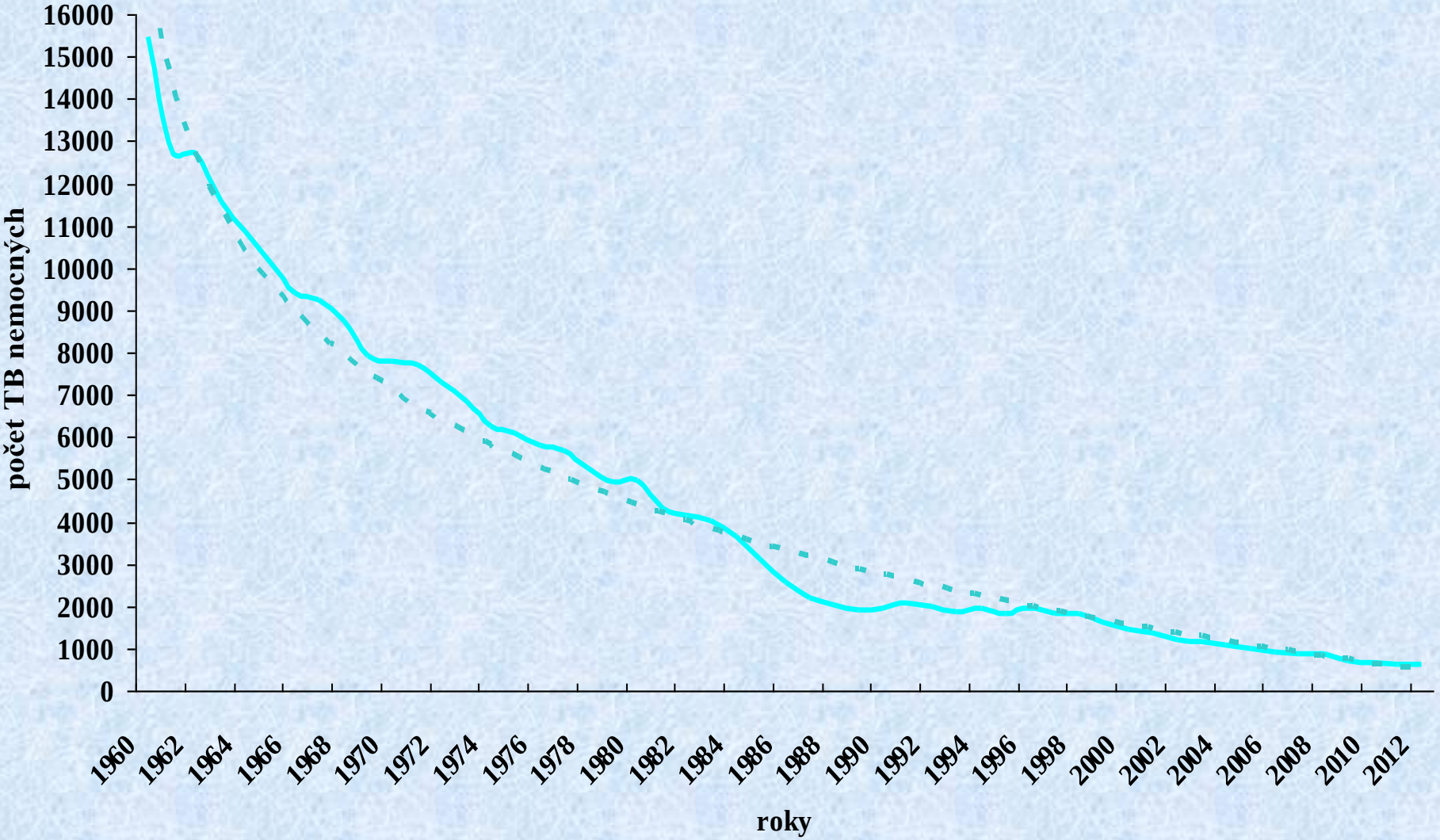
WHO: Global tuberculosis report 2018

Epidemiology of TB
Czech Republic

- Decrease of notified cases since sixties
- 2017: Incidence rate 4.8 per 100 000 inhab.
- WHO: CR is low TB incidence country

» Národní jednotka dohledu nad tuberkulózou
» Ústav zdravotnických informací a statistiky České republiky

Epidemiologic situation in TB Czech Republic 1960-2012



Notification of TB in Czech Republic, 2005 – 2014

ROK	CELKEM	/100 000 OBYVATEL
2005	1007	9,9
2006	973	9,5
2007	871	8,4
2008	879	8,4
2009	710	6,8
2010	680	6,5
2011	609	5,8
2012	611	5,8
2013	502	4,8
2014	514	4,9
2015	518	4,9
2017	505	4,8

Zdroj: Národní registr tuberkulózy

Migration

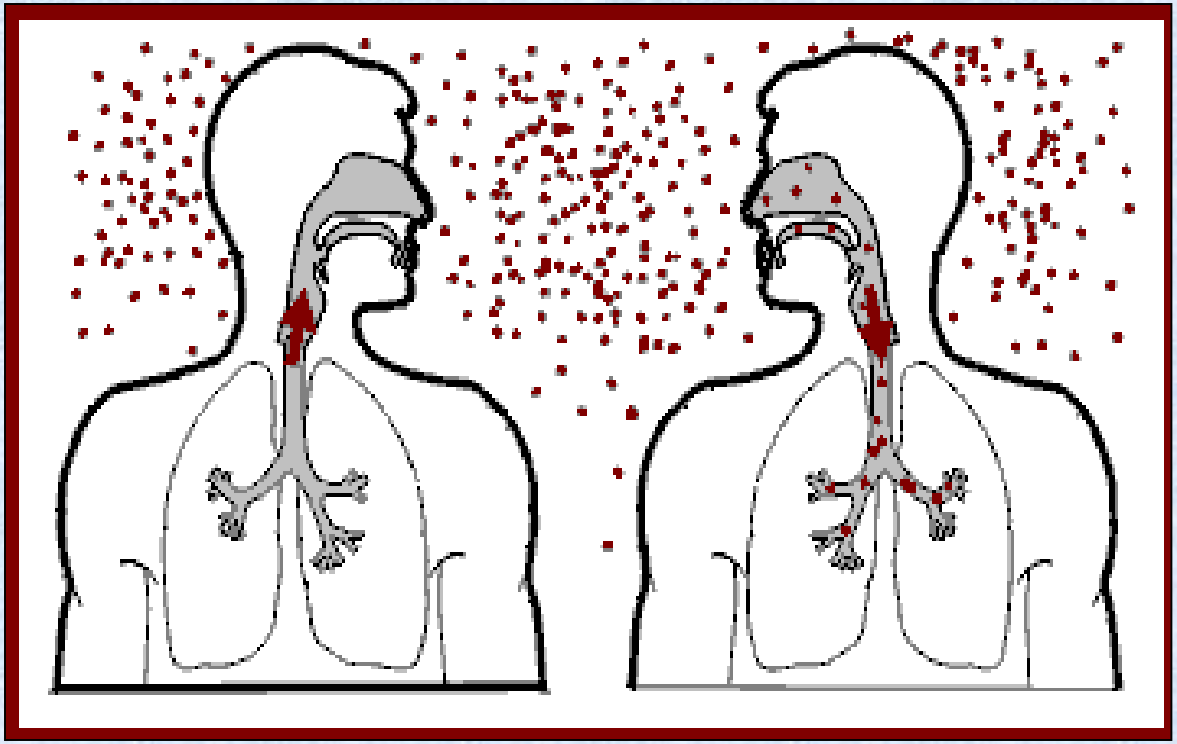
Migration from high to low incidence countries in Europe has an important influence on the epidemiology of tuberculosis

Migration within Europe is likely to play an increasing role in the tuberculosis situation

Determinants characteristics and outcome of tuberculosis in the foreign population should be be closely monitored

Euro TB - April 2000

Transmission and Pathogenesis of TB



Transmission of *M. tuberculosis*

- Spread by droplet nuclei
- Expelled when person with infectious TB coughs, sneezes, speaks, or sings
- Close contacts at highest risk of becoming infected
- Transmission occurs from person with infectious TB disease (not latent TB infection)

Probability TB Will Be Transmitted

- Infectiousness of person with TB
- Environment in which exposure occurred
- Duration of exposure
- Virulence of the organism

Pathogenesis

- *M. tb* ingested by macrophages in alveoli
- May survive and multiply
- Spread by lymphatics to hilar nodes
- Cellular immunity develops 2-12 wks after infection and usually limits *M. tb* growth in granulomas

Pathogenesis

- 10% of infected persons with normal immune systems develop TB at some point in life, with half within the first 2 years

- HIV strongest risk factor for development of TB if infected

  risk of developing TB disease 7% to 10% each year

- Certain medical conditions increase risk that TB infection will progress to TB disease

Common Sites of TB Disease

- Lungs
- Pleura
-
- Central nervous system
- Lymphatic system
- Genitourinary systems
-
- Bones and joints
- Disseminated (milliary TB)

Evaluation for TB

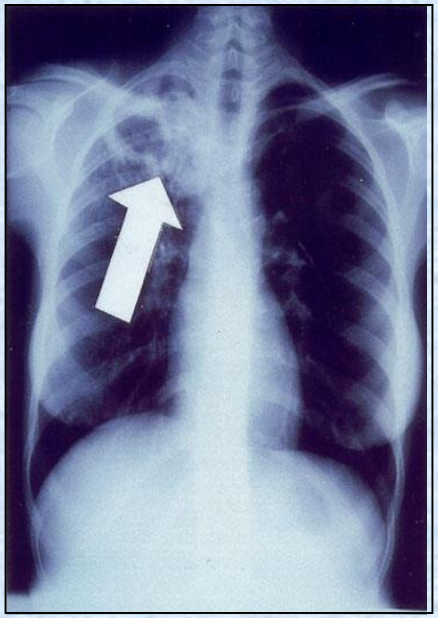
- Medical history
  - Symptoms of disease
  - History of TB exposure, infection, or disease
  - Past TB treatment
  - Demographic risk factors for TB
  - Medical conditions that increase risk for TB
- Physical examination
- Tests of LTB
- Chest radiograph
- CT of the chest
- Bacteriologic or histologic exam
- Methods of genetic analysis
- Treatment test

Symptoms of Pulmonary TB

- Respiratory symptoms
  - Productive, prolonged cough
  - Chest pain
  - Hemoptysis
- Systemic symptoms
  - Fever
  - Chills
  - Night sweats
  - Appetite loss
  - Weight loss
  - Easy fatigability

Chest Radiograph

- Abnormalities often seen in apical or posterior segments of upper lobe or superior segments of lower lobe
- May have unusual appearance in HIV-positive persons
- Cannot confirm diagnosis of TB



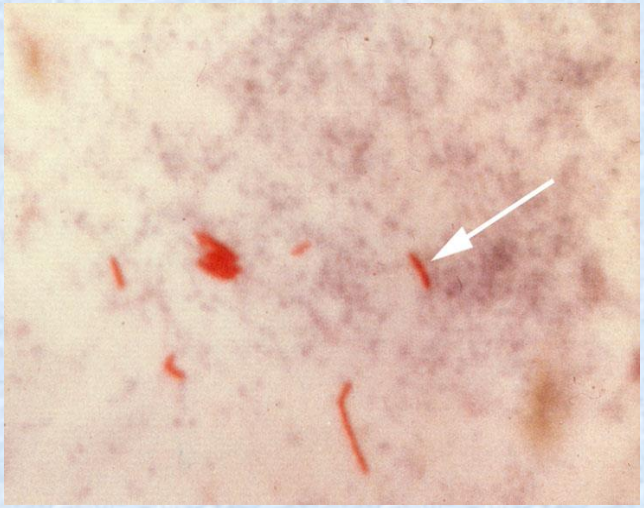
Arrow points to cavity in patient's right upper lobe.

Specimen Collection

- Obtain 3 sputum specimens for smear examination and culture
- Persons unable to cough up sputum, induce sputum, bronchoscopy or gastric aspiration
- Follow infection control precautions during specimen collection

Smear Examination

- Strongly consider TB in patients with smears containing acid-fast bacilli (AFB)
- Results should be available within 24 hours of specimen collection
- Presumptive diagnosis of TB



AFB (shown in red)

Cultures

- Use to confirm diagnosis of TB
- Culture all specimens, even if smear negative
- Results in 4 to 14 days when liquid medium systems used

Colonies of *M. tuberculosis* growing on media

Nucleic Acid Amplification Tests

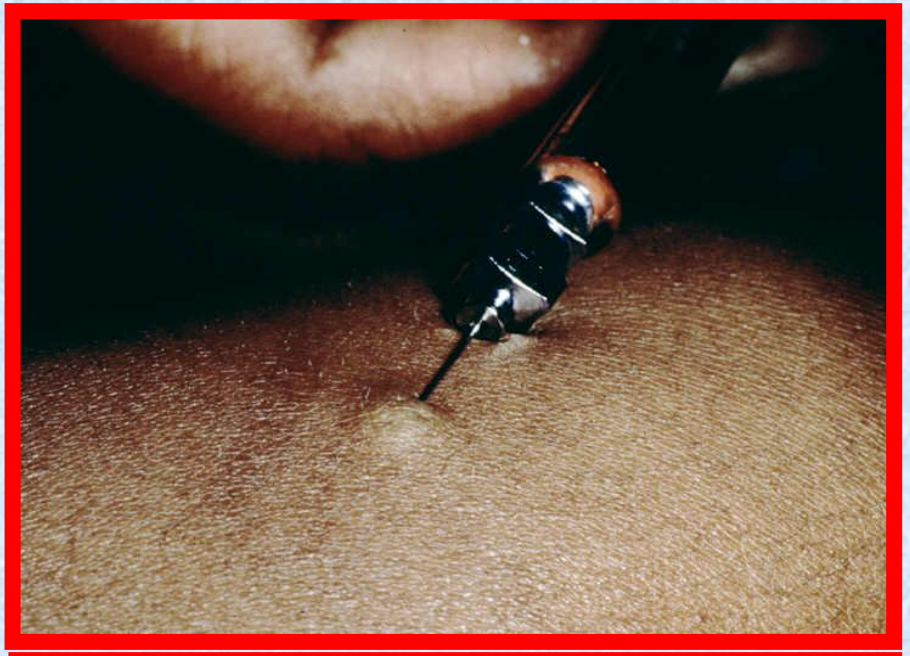
- Enhanced Amplified Mycobacterium Tuberculosis Direct Test (E-MTD), (Gen-Probe®)
  - sensitivity of >95% for detecting M. tuberculosis bacteria in respiratory specimens from AFB-smear positive TB suspects
  - 75% to 90% for detecting *M. tuberculosis* bacteria in respiratory specimens from AFB-smear negative TB suspects.
- Amplicor® Mycobacterium Tuberculosis Test (Amplicor) (Roche®)
  - sensitivity of >95% for detecting *M. tuberculosis* bacteria in respiratory specimens from AFB-smear positive TB suspects
  - sensitivity of 60% to 70% for detecting M. tuberculosis bacteria in respiratory specimens from AFB-smear negative TB suspects.

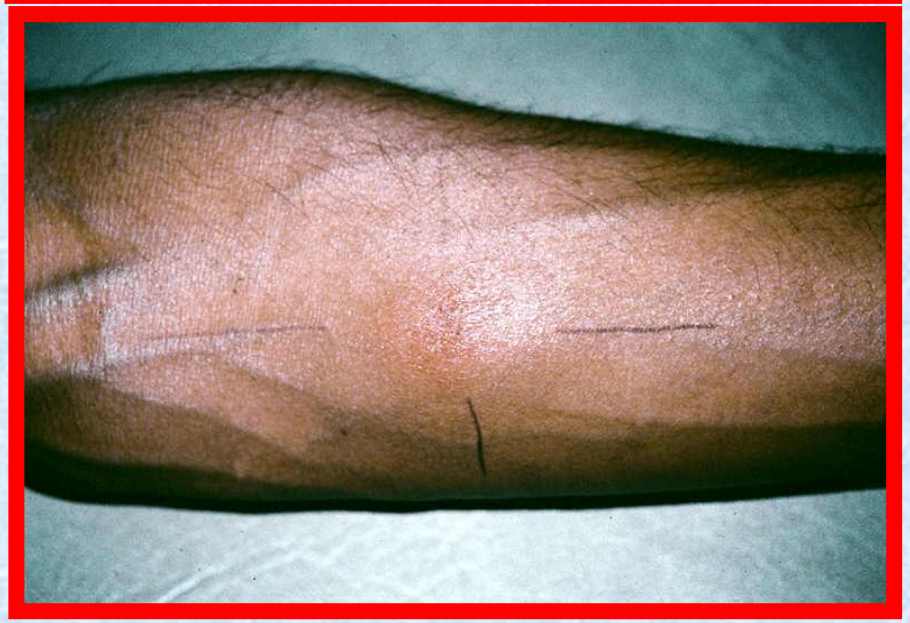
Diagnosis of latent TB infection

- Tuberculin skin test (TST)
- IGRA tests

TST (Mantoux II)

- 0.1 ml intermediate strength PPD in TB syringe
- Intradermal injection on volar aspect of forearm
- Examine site in 48-72 hours
- Measure induration in millimeters at its widest transverse diameter





Mantoux II test (TST) Interpretation in Czech Republic

- In vaccinated population
- One level interpretation
- More than 5 mm is positive
- 15 mm and more is suspicious from active TB

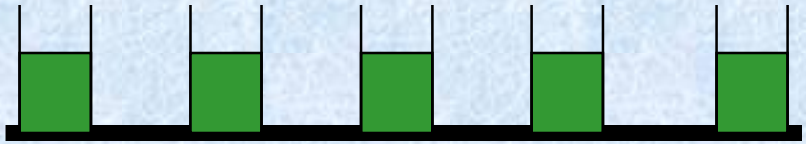
Interferon-γ release assays (IGRA)

- **QuantiFERON -TB Gold In-Tube**
- **T-SPOT.TB**

Quanti-FERON-TB® Test

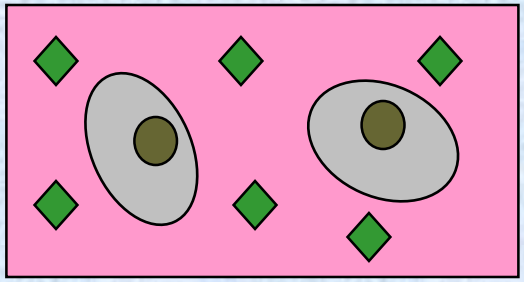
Collect blood → Dispense blood into wells

Add stimulation antigens to blood



Nil antigen | Hu PPD | Av PPD | Rec antigens | Mitogen control

Specific T cells respond and produce gamma-interferon



→ ELISA

Anti-TNF alpha therapy

- All patients should be screened for LTBI before being given anti-TNF alpha therapies
  - Etanercept (ENBREL), Infliximab (REMICADE), Adalimumab (HUMIRA)
- Screening should be based on history, chest x-ray and IGRA
- Preventive treatment should be given where LTBI is suspected as a result of:
  - Positive IGRA
  - Abnormal x-ray suggesting TB which was not adequately treated
  - History of significant prior exposure

Latent TB Infection Treatment Regimens (CDC)

Drugs	Duration	Interval	Minimum doses
Isoniazid	9 months	Daily	270
		Twice weekly*	76
Isoniazid	**6 months**	**Daily**	**180**
		Twice weekly*	52
Isoniazid and Rifapentine	3 months	Once weekly*	12
Rifampin	4 months	Daily	120

TUBERCULOSIS TREATMENT

Prompt and efficient treatment of active tuberculosis is a key element in the prevention of spread of TB infection.

Treatment of TB – combination of antituberculous drugs

<u>Inicial phase /2 months/:</u>

isoniazid, rifampicin, etambutol, pyrazinamid;
relapse + streptomycin

Continous phase /4 months/:

isoniazid, rifampicin; relapse + etambutol

Basic TB Disease Treatment Regimens (CDC)

Preferred Regimen	**Alternative Regimen**	**Alternative Regimen**
Initial Phase Daily INH, RIF, PZA, and EMB* for 56 doses (8 weeks)	Initial Phase Daily INH, RIF, PZA, and EMB* for 14 doses (2 weeks), then twice weekly for 12 doses (6 weeks)	Initial Phase Thrice-weekly INH, RIF, PZA, and EMB* for 24 doses (8 weeks)
Continuation Phase Daily INH and RIF for 126 doses (18 weeks)	Continuation Phase Twice-weekly INH and RIF for 36 doses (18 weeks)	Continuation Phase Thrice-weekly INH and RIF for 54 doses (18 weeks)

MDR TB

(multidrug resistant tuberculosis)

- M. TB resistant to INH and RIF
- Treatment with 2 nd line drugs
- Duration of therapy: 18-24 months

XDR TB

(extensively drug resistant tuberculosis)

- M. TB resistant to INH and RIF plus resistant to any quinolone and at least one of the injectable second-line anti-TB drugs: kanamycin, capreomycin, or amikacin.

Xpert MTB/RIF

- an automated, cartridge-based nucleic amplification assay
- for the simultaneous detection of TB and rifampicin resistance
- directly from sputum in under two hours.

Second line anti-TB drugs

Group name	Anti-tuberculosis agent	Abbreviation
Second-line parenteral agent (injectable anti-tuberculosis drugs)	kanamycin amikacin capreomycin	Km Amk Cm
Fluoroquinolones	levofloxacin moxifloxacin gatifloxacin ofloxacin	Lfx Mfx Gfx Ofx
Oral bacteriostatic second-line anti-tuberculosis drugs	ethionamide prothionamide cycloserine terizidone *p*-aminosalicylic acid	Eto Pto Cs Trd PAS
Group 5 drugs	clofazimine linezolid amoxicillin/clavulanate thioacetazone clarithromycin imipenem	Cfz Lzd Amx/Clv Thz Clr Ipm

NB. Other drugs not generally considered as second-line anti-tuberculosis agents were also used to treat drug-resistant TB in some of the cohorts included in this analysis. These included the parenteral agent *viomycin*, the fluoroquinolones *ciprofloxacin* and *sparfloxacin*, as well as *azithromycin*, *roxithromycin*, *high-dose isoniazid* and *thioridazine*, which were included under the Group 5.

Second-line anti-TB regimen

- Pyrazinamide
- Injectable drug (kanamycin or amikacin or capreomycin)
- Fluoroquinolone (preferably later-generation)
- Ethionamide or prothionamide
- Cycloserine or PAS

- **Intensive phase 8 months**
- **Total treatment duration 20 months** (new cases)

Emergence and Spread of Extensively and Totally Drug-Resistant Tuberculosis, South Africa

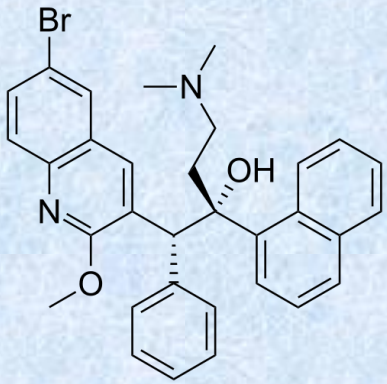
- Situation
  - TB incidence (incl HIV) 971/100,000
  - MDR 1.8% new / 6.7% pretreated cases
  - 13,000 MDR TB cases
  - 46% MDR cases treated
  - Cure rate MDR < 50%, XDR 19%

- 93% XDR atypical Beijing isolates were resistant to 10 anti-TB drugs + PAS
- emergence of **totally drug-resistant TB**

Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 19, No. 3, ***March 2013***

Bedaquiline

(Sirturo, Janssen)



- The first new anti-TB drug in more than forty years
- Approved by FDA on December 28, 2012
- Mode of action: ATP synthase inhibition
- The distinct target of bedaquiline ensures the absence of cross-resistance with existing anti-TB drugs
- Especifically approved to treat MDR-TB
- Addition to current treatment regimens results in a faster sputum culture conversion and fewer treatment failures
- Bedaquiline will improve treatment outcomes of MDR-TB

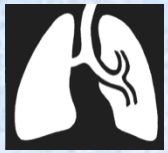
Pathogenesis of extrapulmonary TB

- Extrapulmonary TB is postprimary (with exception of generalised TB)
- Mycobacteria seeds most often in lung apices, metaphyses of long bones, in renal cortex (in sites with high O2 tension and perfusion)
- Rarely in liver, spleen and bone marrow
- Progression in impairment of immunity

Diagnosis of extrapulmonary TB

- Diagnosis is difficult (and often late)
- Estimation of risk factors
- Site specific symptoms, fever of unknown origin
- Limited significance of tuberculin skin test
- Imaging methods
- Biopsy – histology, culture and PCR of M. TB.
- Therapy may be presumptive in life threatening conditions (TB of CNS, generalised TB)

Superficial TB lymphadenitis



- Neck lymph nodes are involved in 70%
- Axillary and inguinal lymph nodes in 30%
- Usually presents with a unilateral, painless, non-tender neck mass
- With time the nodes may become fluctuant and drain spontaneously
- The best diagnostic procedure is excisional biopsy (diagnosis in 80% of cases)
- Fine needle aspiration biopsy is diagnostic in 60% of cases.
- Incisional biopsies are discouraged because of the risk of sinus tract formation at the biopsy site

Superficial TB lymphadenitis

- In children 50% of TB lymphadenitis is caused *M. avium*
- Treatment is according to standard protocol
- Nodes can appear afresh or enlarge during treatment
- Fluctuation discharge, sinus formation and scar breakdown occur in a minority
- At the end of treatment, 10% may be left with residual nodes
- Surgical procedures, other than diagnostic should be reserved for the relief of discomfort caused by enlarged nodes

Bone and joint TB

- TB involves mataphyses and joints – sites with richest blood supply
- Spinal or vertebral TB
  - the classic form (spondylodiscitis)
  - atypical form (spondylitis without disc involvement)

  Complications:

  Cold abscess – paravertebral pus collection

  Spinal angulation

  Compression and vascular damage to the spinal cord
- TB arthritis - usually a mono-arthritis affecting large joints
- Other sites involvement is very infrequent
- Th: AT, orthopedics surgery currative or palliative

Disseminated TB (milliary disease)

- Hematogennous spread of TB bacili
- Granulomas 1-2 mm in d.
- Early dissemination (nonvaccinated or immunocompromised children)
- Late dissemination (in old age, HIV infection)
- Non-specific presentation: fever, anorexia, weight loss and weakness
- Fever of unknown origin

Disseminated TB: diagnosis and therapy

- Imaging methods: Chest X-ray and CT, abdominal ultrasound
- Eye fundus examination
- Blood culture, bone marrow aspiration, liver biopsy, lumbar puncture, bronchoscopy, lung biopsy
- Treatment: antituberculous chemotherapy + glucocorticoids

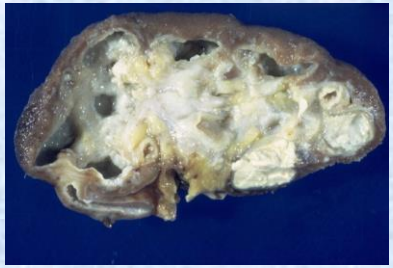
CNS TB

- Initial lesion is a tubercle in the superficial cortex or meninges that ruptures into the subarachnoid space
- Brain damage results from the effects of the granulomatous basal exudate
- Raised intracranial pressure with obstructive hydrocephalus
- Basal ganglia and brainstem infarction secondary to periarteritis of the blood vessels
- Clinical course: headache, fever, meningismus, cranial nerve palsies, seizures, coma and death

CNS TB

- Diagnosis:
  - clin. presentation
  - lumb. puncture – low glucose, elev. protein levels, lymphocyte predominance, AFB smear and culture, PCR M. TB
  - imaging
- Treatment: antituberculous chemotherapy + glucocorticoids, neurosurgical intervention
- Prognosis: 25% morbidity, i.e. permanent neurologic deficit, and 25% mortality

Genitourinary TB



- Kidney – caseating granulomas of cortex, later involvement of calices and pelvis
- Ureter, bladder

- Prostate, seminal vesicles, epididymis and testes

- Fallopian tubes/ovaries, endometrium/cervix, vulva

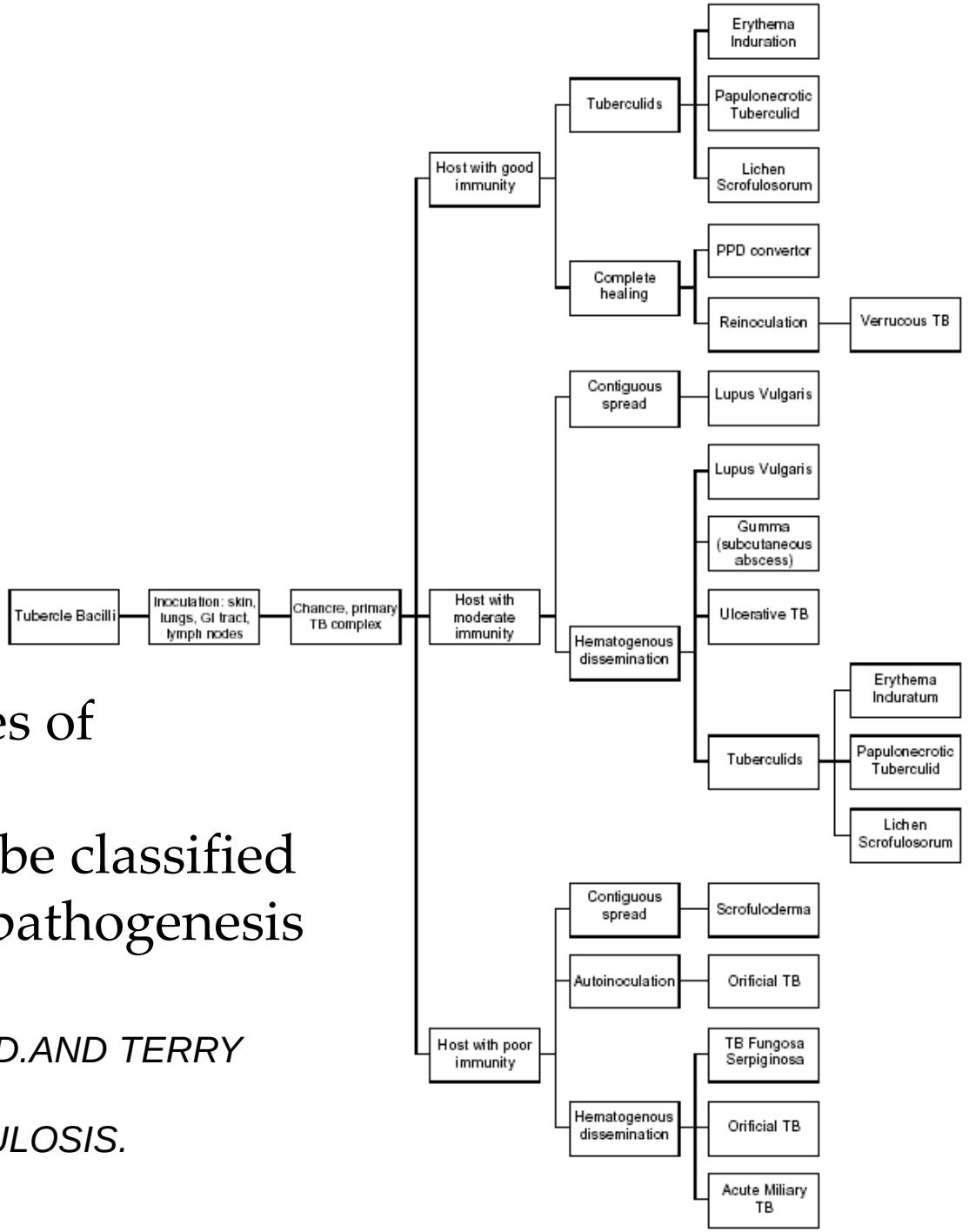
Genitourinary TB

- Presentation: 20% of patients asymptomatic, dysuria, back pain, fever
- Lab: aseptic pyuria, culture and PCR for M. TB – 10 specimen
- Imaging methods: urography (ulcerations, deformations), ultrasound, CT
- Endoscopic methods, puncture biopsy
- Th: standard regimen 6-9 m., reconstructive surgery

Cutaneuous TB

- Classification based on
  - clinical morphology
  - etiology
  - the immune status of the host
- Problems
  - morphologic classification is unsatisfactory. Similarly appearing skin lesions can have multiple causes and can differ histologically
  - classifications based on etiology or immune status are not helpful clinically

General pathogenesis of cutaneous tuberculosis



"The complexities of cutaneous tuberculosis can be classified and the general pathogenesis described"

JAMES W. STEGER, M.D.AND TERRY L. BARRETT, M.D. CUTANEOUS TUBERCULOSIS. In Military Dermatology

CLASSIFICATION OF CUTANEOUS TUBERCULOSIS

Stage	Source	Mode	Histology	Course	Disease	Immunity	Bacilli
Primary	Exogenous	Inoculation	Nonspecific	Localized	Chancre	Developing	+++
			TB specific	Localized	Primary TB complex	Good	+?
			TB specific	Localized	Lupus vulgaris	Moderate	++
			TB specific	Progressive	TB fungosa serpiginosa	Poor	+++
			TB specific	Generalized	Miliary TB	Poor	+++
Secondary	Exogenous	Reinoculation	TB specific	Localized	TB verrucosa cutis	Good	+/−
			TB specific	Progressive	TB cutis orificialis	Poor	+++
	Endogenous	Contiguous	TB specific	Localized	Lupus vulgaris	Moderate	++
			TB specific	Localized	Scrofuloderma	Poor	+++
		Autoinoculation	TB specific	Localized	TB verrucosa cutis	Good	+/−
			TB specific	Progressive	TB cutis orificialis	Poor	+++
		Hematogenous	TB specific	Localized	Lupus vulgaris	Moderate	+++
			TB specific	Localized	Gumma (subcutaneous abscess)	Moderate	++
			TB specific	Localized	Ulcerative TB	Moderate	++
			TB specific	Progressive	TB fungosa serpiginosa	Poor	+++
			TB specific	Progressive	TB cutis orificialis	Poor	+++
			TB specific	Generalized	Miliary TB	Poor	+++
Tuberculid	Endogenous	Hematogenous	Variable	Localized	Erythema induratum	Moderate-to-good	−/+
			Variable	Scattered crops	Papulonecrotic tuberculid	Moderate-to-good	−/+
			Variable	Generalized	Lichen scrofulosorum	Moderate-to-good	−/+

+++: numerous bacilli; ++: some bacilli; +/−: bacilli rarely found; −/+: unusual to find bacilli; +?: variable, depending on time course

TB of other sites

- ENT: inner ear, proc. mastoideus, nose, nasopharynx, paranasal sinuses, salivary glands, oral cavity, tonsiles, lymph nodes
- Eye
- Pericardium
- Adrenals

"Every organ system in the body can be involved with T

Treatment of extrapulmonary TB

- Standard regimen chemotherapy can be extended to 9 months
- Indications of glucocorticoids
  - CNS TB
  - milliary TB with septic shock
  - TB of serous membranes
  - adrenal TB
- Surgical interventions after at least 6 wks of chemotherapy