МИНИСТЕРСТВО ЗДРАВООХРАНЕНИЯ РЕСПУБЛИКИ БЕЛАРУСЬ

УЧРЕЖДЕНИЕ ОБРАЗОВАНИЯ
«ГОМЕЛЬСКИЙ ГОСУДАРСТВЕННЫЙ МЕДИЦИНСКИЙ УНИВЕРСИТЕТ»

Кафедра фтизиопульмонологии

И. В. БУЙНЕВИЧ, С. В. ГОПОНЯКО

ТУБЕРКУЛЕЗ

Учебно-методическое пособие
для студентов 4 и 6 курсов факультета по подготовке специалистов
для зарубежных стран медицинских вузов

TUBERCULOSIS

Teaching workbook
for 4th and 6th year students
of the Faculty on preparation of experts
for foreign countries of medical higher educational institutions

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Рецензенты:

кандидат медицинских наук, доцент,
заведующая кафедрой фтизиопульмонологии
Белорусского государственного медицинского университета
Г. Л. Бородина;

кандидат медицинских наук, доцент,
заведующая кафедрой фтизиопульмонологии
Гродненского государственного медицинского университета
Е. Н. Алексо

Буйневич, И. В.

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CONTENT

ABBREVIATIONS

ACE — angiotensin converting enzyme
ADA — adenosine deaminase
AFB — acid fast bacillus
BAL — bronchoalveolar lavage
BCG — bacilleCalmette-Guérin
CBC — complete blood count
CNS — central nervous system
COPD — chronic obstructive pulmonary disease
CSF — cerebrospinal fluid
CT — computer tomography
DNA — desoxyribonucleic acid
DOTS — Directly Observed Treatment, Short-course
DST — drug susceptibility testing
DR — drug resistance
ECG — electrocardiography
ESR — erythrocyte sedimentation rate
HIV/AIDS — human immunodeficiency virus/acquired immunodeficiency syndrome
IFN-γ — interferon gamma
IGRAs — IFN-γ release assays
LTBI — latent tuberculosis infection
MBT — Mycobacterium tuberculosis
MDR — multi- drug resistance
MRI — magnetic resonance imaging
NTP — national tuberculosis program
PCR — polymerase chain reaction
PPD — purified protein derivative
PTB — pulmonarytuberculosis
RNA — ribonucleic acid
TST — tuberculin skin test
TB — tuberculosis
WBC — white blood cells
WHO — World Health Organization
UV — ultraviolet
XDR — extended drug resistance

1. ETHICAL AND DEONTOLOGICAL ASPECTS IN TB HOSPITAL. EPIDEMIOLOGY OF TUBERCULOSIS. ETIOLOGY AND PATHOGENESIS OF TUBERCULOSIS

1.1. Ethical and deontological aspects in TB hospital

Medical ethics studies social duties of physician, a specific essence, patterns of development and the formation of medical morality, physician's attitude to the general principles of morality and society.

Features of medical ethics:

1) consider the physician's attitude to the person with impaired health or risk of disorders;

2) examine the features of development, dependence medical moral from the conditions of medical practice;

3) covers not only issues relating to the doctor-patient, but also defines a norm physician behavior in everyday life, its high culture, physical and moral cleanliness.

Medical deontology — set of relevant professional, ethical and legal principles and rules that make up the concept of medical debt.Governed by guidelines and job descriptions.

Basic requirements and problems of medical ethics and medical deontology:

1. Physician must possess certain qualities: 1) humanism — the love of the people; 2) high moral culture; 3) eypatiya — the ability to empathize with the psychological state of the other; 4) intelligence, erudition; 5) charity; 6) duty, honor and conscience; 7) sense of bedside manner

2. Physician in his profession interacts with themselves different areas of social life (physician — society, physician — state, physician — right, physician — law, physician — patient, physician — physician, physician and his attitude to yourself), which has an impact on his career.

3. The patient's life depends on the physician, so the physician must strive not to make mistakes (diagnostic, prognostic, therapeutic, deontological, etc.)

4. Modern medical ethics and deontology has a number of outstanding issues: collegiality in the work of the doctor; terminally ill people and euthanasia; extension of life ill newborns; abortion issue; successes of modern biomedicine (genetic engineering); problem of transplantation of human organs.

How to improve treatment compliance

Organizational measures are aimed at providing management of patients until cure. The two main obstacles that need to be overcome are the length of treatment (several months) and the constraints related to directly observed treatment.

In order to improve compliance, it is necessary to:

1. Form in patient adherence to long treatment and observation. To explain obligation to undergo a complete course of treatment after symptoms disappearing.

2. Explain the necessity of long-lasting hospitalization of smear-positive patients and thorough treatment following after discharge

3. Help the patient to realize possibilities of anti-TB drugs side-effects.

4. Communicate with patient's relatives in order to keep the patient up.

Communication with the patient

Health education is an ongoing process that allows health staff to inform patients about their illness and its treatment, and to respond to any questions that might be asked by patients and their families. It should aid in creating an immediate rapport with the patient. The first interview with the patient is often the key to how treatment progresses. Following this first contact, every encounter with the health staff should be seen as an opportunity to strengthen communication and to improve the health education of the patients and their families.

What is the most important information?

- Pulmonary tuberculosis is a serious disease that can nevertheless be completely cured when treatment is taken correctly.
- The treatment must be taken for at least 2 months in the presence of a health worker. The patient should not see this obligation as a punishment but as a necessity in order to ensure correct treatment, as well as an opportunity for daily contact with the health personnel in order to ask questions or resolve any problems that may occur.
- Pulmonary tuberculosis is infectious before it is treated, but it is no longer so after the second week of treatment if the drugs have been taken correctly by the patient.
- Treatment efficacy is monitored during appointments, by clinical examination and above all by bacteriological examinations in the case of pulmonary tuberculosis.
- Children aged under 5 years living in the same household as a patient with pulmonary tuberculosis must be brought to the control center to receive preventive therapy or treatment if they have tuberculosis.
- The other members of the household should present to the nearest health facility or the tuberculosis control center for examination.

It is nevertheless difficult for the patient to assimilate all of the information during the first interview: this is why all of the health personnel, and particularly the treatment supervisor, must be trained to give the information repeatedly and to respond to the questions that the patient will inevitably ask. Moreover, it is valuable to encourage interaction among patients as they visit the health facility, as this type of communication is often much more effective than contact with the health personnel alone.

What are the most common questions asked by patients or their families?

The questions are most often about infection, but they are expressed in different ways:

- Can the patient eat with his or her family as before?
- Can the patient continue to live normally with his or her spouse?
- Can the patient continue to work?

All responses should be clear: the patient can live normally in the community as long as treatment is strictly adhered to. These responses also aid in encouraging not only the patients, but also their families, to continue to take their treatment regularly and to attend follow-up appointments until cure. A strong personal bond between the health staff and their patients, and also their families, is thus created and reinforced over time. This relationship will aid in identifying the problems of patients who default and in together finding a solution which will enable them to continue to take their treatment regularly: e. g. changes in intervals between drug delivery, transfer of a patient to another treatment center that is closer to the patient's workplace, or temporarily to another center during a holyday.

1.2. The global burden of tuberculosis, TB infection, disease and death rates in the world

If efforts were not made to improve and expand tuberculosis control programs annually more than 8 million cases were expected to occur worldwide, of whom 10 % or more would be attributable to the HIV epidemic. About 75% of these cases were in the African Region. About 2 million deaths due to tuberculosis were foreseen.

95 % of individuals with tuberculosis live in the poorest countries: because of the poor health coverage of the population, only a proportion of these patients are detected and treated.

The TB incidence rate at country level ranges substantially, with around 1000 or more cases per 100 000 people in South Africa and Swaziland, and fewer than 10 per 100 000 population in parts of the Americas, several countries in Western Europe, Japan, Australia and New Zealand. The majority of cases worldwide annually are in the South-East Asia (29 %), African (27 %) and Western Pacific (19 %) regions. India and China alone accounted for 26 % and 12 % of total cases, respectively.

Tuberculosis incidence cannot be based only on the incidence of notified cases, which in general is lower than real incidence because only 30–60 % of TB cases are diagnosed and reported. The recent increase in tuberculosis notification rate is associated with migration of populations from countries with a high tuberculosis burden and, to a lesser extent, with the emergence of HIV epidemic.

Globally about in half million people annually MDR-TB developesand about 200 000 deaths is estimated from MDR-TB. Tuberculosis remains to be the first reason of death in HIV-infected patients.

Most TB cases and deaths occur among men, but TB remains among the top three killers of women worldwide. About 25 % of the estimated new TB cases worldwide are women. Annually almost 500 000 TB deaths are estimated among women; about 30 % of them are HIV-positive. Women are the half of the HIV-positive people who died from TB.

Annually about 500 000 TB cases are estimated among children (under 15 years of age) and 70 000 TB deaths (among HIV-negative children) — 6 and 8 % of the global totals, respectively.

1.3. Etiologic agent of tuberculosis. Microscopic morphology of Mycobacterium tuberculosis. Metabolic capabilities, nutritional and environmental requirements for growth. MBT generation time. Resistance to physical and chemical challenges

Tuberculosis (TB) is the disease caused by bacteria of the Mycobacterium tuberculosis complex, which includes the clinically relevant species, M. tuberculosis, M. bovis, and M. africanum. These organisms are also known as tubercle bacilli (because they cause lesions called tubercles) or as acid-fast bacilli (AFB). Although M. tuberculosis is the most common cause of TB worldwide, both M. bovis and M. africanum can produce clinically indistinguishable forms of disease.

Etiologic agent

M.tuberculosis is a rod-shaped, non-spore-forming, thin aerobic bacterium measuring 0,5 by 0,3 m. They are grouped in the suprageneric rank of actinomycetes that, unusually, have a high content (61–71 %) of guanine plus cytosine (G+C) in the genomic desoxyribonucleic acid (DNA), and a high lipid content in the wall, probably the highest among all bacteria.

Table 1.1 — Lineage of the agents of TB

Kingdom	Bacteria
Phylum	Actinobacteria
Class	Actinobacteria
Order	Actinomycetales
Suborder	Corynebacterineae
Family	Mycobacteriaceae
Species	M. tuberculosis M. bovis M. africanum

The taxonomic status of some members of the complex is still uncertain.

Mycobacteria are often neutral on Gram's staining. The bacilli can't be decolorized by acid alcohol; this characteristic justifies their classification as acid-fast bacilli (AFB). Acid fastness is due mainly to the organisms' high content of mycolic acids, long-chain cross-linked fatty acids, and other cell-wall lipids. Several mycolic acids in the envelope structure distinguish the mycobacteria. These quirky lipids may act as carbon and energy reserves. They are also involved in the structure and function of membranes and membranous organelles within the cell. Lipids constitute more than half of the dry weight of the mycobacteria.

The waxy coat confers:

✓acid fastness, extreme hydrophobicity, resistance to injury, including that of many antibiotics;

✓slow growth rate of some species by restricting the uptake of nutrients.

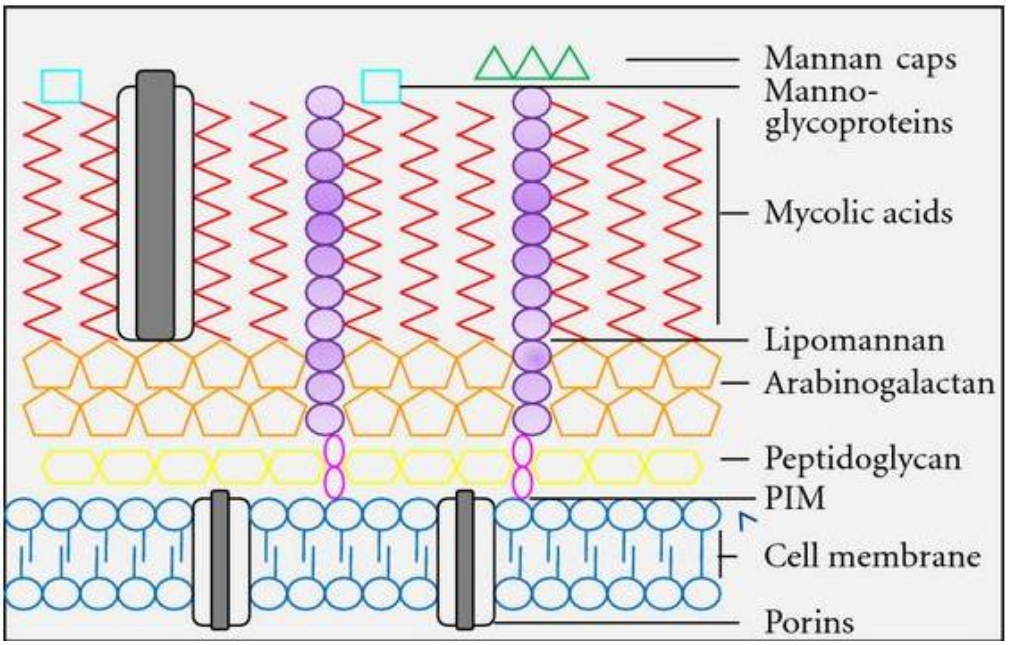


Figure 1.1 — Cell wall structure

The microscopic appearance does not allow the differentiation of the pathogenic agents of TB, mainly M. tuberculosis, from other mycobacteria although some characteristics may be indicative. In smears stained with carbol fuchsin or auramine and examined under light microscope, the tubercle bacilli typically appear as straight or slightly curved rods.

Bacterial cell contents as well ribosomes and DNA filaments. The envelope is composed of the *plasma membrane*, *a cell wall,* and *an outer capsule like layer.*

The ***cytoplasmic membrane*** provides osmotic protection, regulates the traffic of specific solutes between the cytoplasm and the environment. The membrane contains proteins involved in metabolic processes and energy generation. The enzymes intervene in cell wall and membrane synthesis, cell division and DNA replication.

The membrane is surrounded by a ***cell wall*** that protects the cell contents, provides mechanical support and is responsible for the characteristic shape of the bacterium. The mycobacterial cell wall is unique among prokaryotes. In the mycobacterial cell wall, lipids (high molecular weight fatty acids called *mycolic acids*) are linked to underlying *arabinogalactan* and *peptidoglycan*which is responsible for the shape-forming. Another molecule in the mycobacterial cell wall, *lipoarabinomannan*, is involved in the pathogen-host interaction and facilitates the survival of M. tuberculosis within macrophages.There are also proteins (*porins*) forming hydrophilic channels that permit the passive passage of aqueous solutes through the mycolic acid layer.

While growing in a static liquid culture or within a human cell, MBT accumulates an unboundbioactive ***pseudo-capsule*** which promotes the better cell wall permeability. When the medium is disturbed, the capsule separates, leaving the lipophilic surface with high protective characteristics exposed.

Cell wall of virulent MBT contains a special glycolipid ***cord factor*** due to which bacteria arrange in braided bunches in smear and produce rough textured colonies on solid media. In contrast, non-virulent mycobacteria and tubercle bacilli attenuated by prolonged cultures usually develop smooth colonies on solid media and distribute randomly when smeared. The recognition of these two peculiarities, ***cording and crumbly colony formation***, allows the presumptive distinction of M. tuberculosis from other mycobacteria in cultured specimens and even in sputum smears. Cord factor provides the pathogenicity, toxicity and protection against the host response.

Genome structure

Genome of MBT has been sequenced in 1998. Genome size of M. tuberculosis is more than 4mln base pairs long with 4043 genes encoding 3993 proteins and 50 genes encoding RNAs; its high guanine+cytosine content (65,6 %) is indicative of an aerobic lifestyle.M tuberculosis is one of the largest known bacterial genomes.

About 250 genes are involved in fatty acid metabolism, with 39 of these involved in generating the waxy coat. Such large numbers genes show the evolutionary importance of the waxy coat to pathogen survival. Over half of the genes have arisen as a result of gene duplication which playes an important role in genome plasticity. Unlike most bacteria which have multiple copies of the rRNA genes, MBT contains a single one. This explains why single mutations in the ribosomal RNA genes result in resistance to protein synthesis inhibitors (rifampicine).

Nutritional and environmental requirements for growth

M. tuberculosis is ***mesophile*** and ***neutrophile*** as its multiplication is restricted to conditions offered by warm-blooded animals: about 37ºC and a neutral pH.

MBT is ***obligate aerobe*** but in unfavorable conditions metabolism may shift from an aerobic to one that is more microaerophilic and utilizes lipids (which leads to cell wall disorganization and L-form formation). This is a highly resourceful strategy, not only for pathogenicity but also for persistence. In nature, the bacillus grows most successfully in tissues with high oxygen partial tension, such as the lungs, particularly the well-aerated upper lobes.

In vitro, the members of the M. tuberculosis complex are not fastidious; the medium used by Koch to cultivate M. tuberculosis was simply sterile coagulated blood serum. Albumin, which is normally provided by adding eggs or bovine serum albumin to the culture media, promotes the growth.

Generation time

Under favorable laboratory conditions, M. tuberculosis divides every ***12 to 24 hours.*** This pace is extremely slow compared to that of most cultivable bacteria, which duplicate at regular intervals ranging from about 15 minutes to one hour. The slow growth rate might be partially determined by the cell wall impermeability that limits nutrient uptake.

But ribonucleic acid synthesis was identified to be a major factor associated with the long generation time of the tubercle bacillus. The low multiplication rate explains the typically subacute to chronic evolution of the disease and the long time required to attain visible growth in vitro.

The main achievements for diagnosis have been made through the use of tools that enable the detection of a minimal quantity of bacilli in the media.

Metabolic and biochemical markers

In the laboratory the investigation of ***niacin accumulation***, ***catalase-peroxidase,nitrate reductase***and***urease*** activity allows the distinction of M. tuberculosis complex.

The thermal-labile***catalase-peroxidase*** is a marker of the M. tuberculosis complex. Paradoxically, the catalase is not only self-protective but can also be self-destructive as it activates the anti-TB pro-drug isoniazid. Mutations in the genes encoding the enzyme result in resistance to isoniazid.

Resistance to physical and chemical challenges

Although the tubercle bacillus is not a spore-forming bacterium, it has a remarkable capacity to endure unfavorable conditions. The bacillus is able to circumvent destruction within the macrophages and to limit the access to the bacterial targets of hydrophilic antiseptics and antibiotics.

The bacillus survives to some extent in the acid or alkaline microenvironment as a result of its interaction with the defensive mechanism of the host, as well as the acid contents of the stomach.

The microorganism also withstands very low temperatures. Its viability may be increasingly preserved for a long term between 2–4°C to -70°C. On the other hand, the bacilli are very sensitive to heat, sunlight and ultraviolet irradiation. Exposed to direct UV irradiation, moderate loads of tubercle bacilli die in a few minutes.

M. tuberculosis tolerates low oxygen tension. The bacilli may survive for many years in this condition but need a minimal concentration of oxygen to induce the switch into a fermentative metabolism.

1.4. Sources of infection and transmission of the MBT. Risk of infection. Latent tuberculosis infection. Likeliness and risk factors of progression to disease. Natural individual resistance and immune response against M. tuberculosis. Hypersensitivity to MBT components

Sources of infection

The most important source of infection is the patient with TB of the lung, or pulmonary TB (PTB), and who is coughing. This person is usually sputum smear-positive.

Airborne transmission of the MBT

Coughing produces infectious droplet nuclei (infectious particles of respiratory secretions usually less than 5 μm in diameter and containing tubercle bacilli). A single cough can produce 3000 droplet nuclei. Droplet nuclei can also be spread into the air by talking, sneezing, spitting and singing, and can remain suspended in the air for long periods. Direct sunlight kills tubercle bacilli in 5 minutes, but they can survive in the dark for long periods. Transmission therefore generally occurs indoors. Droplet nuclei are so small that they avoid the defenses of the bronchi

and penetrate into the terminal alveoli of the lungs, where multiplication and infection begin. Two factors determine an individual's risk of exposure: the concentration of droplet nuclei in contaminated air and the length of time he or she breathes that air.

Risk of infection

An individual's risk of infection depends on the extent of exposure to droplet nuclei and his or her susceptibility to infection. The risk of infection of a susceptible individual is high with close, prolonged, indoor exposure to a person with sputum smear-positive PTB. The risk of transmission of infection from a person with sputum smear-negative PTB is low, and even lower from someone with extrapulmonary TB .

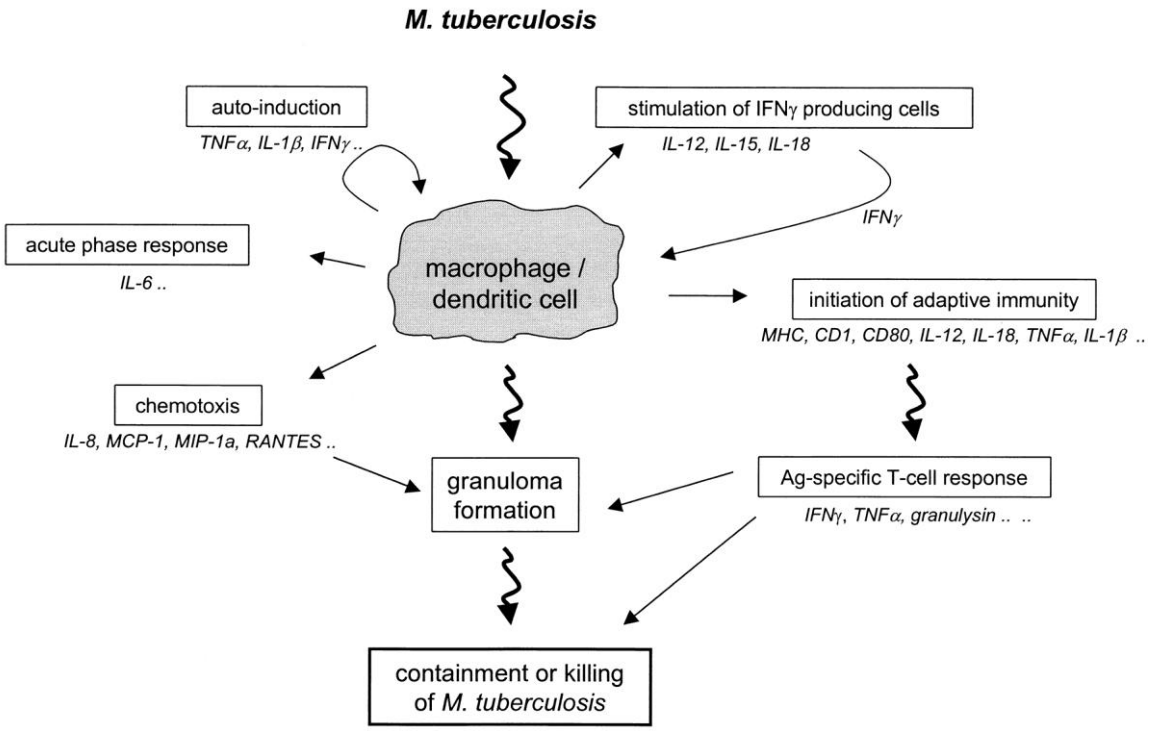


Figure 1.2 — Intracellular cooperation in anti-TB immune response

Risk of progression of infection to disease

Infection with M.tuberculosis can occur at any age. Once infected with M.tuberculosis, a person can stay infected for many years, probably for life. The vast majority (90 %) of people without HIV infection who are infected with M. tuberculosis do not develop TB. In these, asymptomatic but infected individuals, the only evidence of infection may be a positive tuberculin skin test. Infected persons can develop TB at any time. The disease can affect most tissues and organs, but especially the lungs. The chance of developing disease is greatest shortly after infection and steadily lessens as time goes by. Infected infants and young children are at greater risk of developing disease than older people because they have an immature immune system. TB is also more likely to spread from the lungs to other parts of the body in this age group. Children who develop disease

usually do so within two years following exposure and infection. Most do not develop disease in childhood but may do so later in life. Various physical or emotional stresses may trigger progression of infection to disease. The most important trigger is weakening of immune resistance, especially by HIV infection.

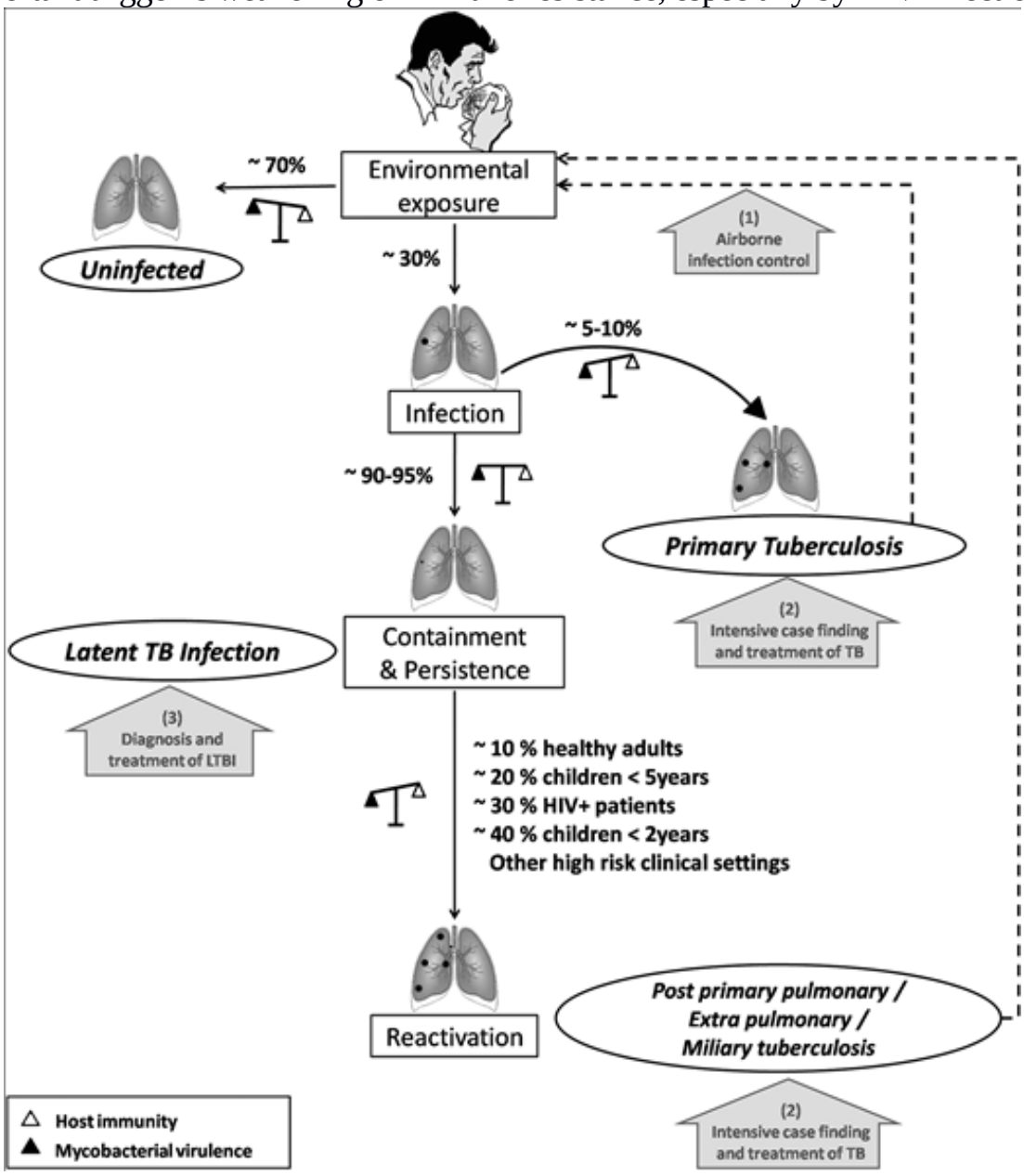


Figure 1.3 — The transmission and natural history of M. tuberculosis

The limits between infection and disease

In developed countries is fairly easy to distinguish TB infection from TB disease. TB infection is characterized by the presence of a positive TST in the absence of symptoms and/or progressive lesions consistent with TB disease. This classification is useful for control strategies in areas of low prevalence of infection and low incidence of new cases. Chemoprophylaxis is indicated for recently infected persons in high risk groups in order to protect them from primary TB.

The application of such control strategies is very difficult in low and middle resource countries with high rates of infection and high incidences of new infectious TB cases. Wide-scale TST and chemoprophylaxis for all tuberculin-positive individuals would be neither innocuous nor cost-effective. Large scale TST testing demands a sophisticated system of production, quality control, distribution, handling and application of reagents. This strategy is not feasible in low resource countries where health attention systems have scarce economic, operational and human resources. In such countries, contact investigation should be introduced more widely after an evaluation of its cost-effectiveness and refined estimates of the likelihood of TB infection and TB disease in different settings. In summary, in low and middle income countries, whenever possible, the control of the contacts should be done during the follow-up period of the index case, and at least all contacts younger than 15 years old (or particularly under 5 years old) with a TST > 10 mm (if not vaccinated with BCG or vaccinated more than two years before), asymptomatic and with normal chest X-ray, should be given prophylactic INH for at least six months.

Table 1.3 — Risk factors for tuberculosis

Medical risk factors	Social risk factors
HIV	Material poor-being andpoor nourishment
Diabetes	Migrants
Corticosteroid usage	Refugees
Cytostatics and chemotherapy	Prisoners
Cachexia of any genesis	Homeless
Malnutrition	Crowded and unfavorable living conditions
Non specific respiratory diseases	Alcohol addicted
Alcohol and narcotic addiction	

1.5. Tuberculosis histology. Granuloma formation and hallmark of tuberculosis. Residual changes after treated tuberculosis

Tuberculosis histology

When delayed hypersensitivity is present, either weeks after the primary infection or during a period of reactivation disease, a different pathologic pattern emerges. The hallmarks are the presence of (1) granulomas (collections of activated blood and tissue-derived macrophages termed epithelioid histiocytes surrounded by a rim of lymphocytes), and (2) caseous necrosis (foci of necrosis and softening at the center of a granuloma). Within the region of caseous necrosis, the contents can liquefy and slough, leaving behind a cavity, another hallmark of tuberculosis. Other features of the granulomas include multinucleated giant cells and often the presence of tubercle bacilli.

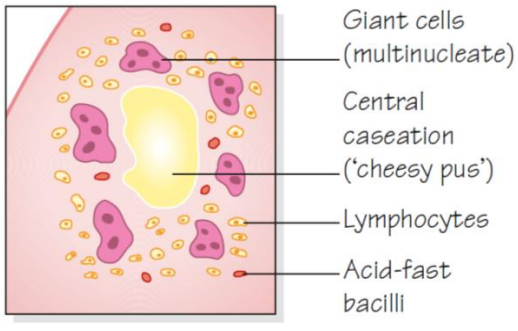


Figure 1.4 — Tuberculous granuloma

A process of healing tends to occur at the sites of disease. Fibrosis or scarring ensues, often associated with contraction of the affected area and deposition of calcium.

Tuberculosis is spread through the bloodstream at the time of primary infection.

When defense mechanisms break down, disease can become apparent at other sites (e.g., liver, kidney, adrenal glands, bones, central nervous system). Spread also occurs to other regions of the lung, either as a result of hematogenous seeding during the primary infection or because of spilling of infected secretions or caseous material into the bronchi and other regions of the lung.

Within the lung, characteristic locations for reactivation tuberculosis are the apical regions of the upper lobes and, to a lesser extent, the superior segment of the lower lobes. These regions have a high PO_2 and relatively less perfusion and thus are believed to be particularly suitable for survival of the aerobic tubercle bacilli.

2. DIAGNOSIS OF TUBERCULOSIS

2.1. Specialty of evaluating patients with tuberculosis. Physical examination of patient

The key to the diagnosis of tuberculosis is a high index of suspicion. Diagnosis is not difficult with a high-risk patient — e. g., a homeless alcoholic who presents with typical symptoms and a classic chest radiograph showing upper-lobe infiltrates with cavities. On the other hand, the diagnosis can easily be missed in an elderly nursing home resident or a teenager with a focal infiltrate.

Often, the diagnosis is first entertained when the chest radiograph of a patient being evaluated for respiratory symptoms is abnormal. If the patient has no complicating medical conditions that cause immunosuppression, the chest radiograph may show typical upper-lobe infiltrates with cavitation. The longer the delay between the on-set of symptoms and the diagnosis, the more likely is the finding of cavitary disease. In contrast, immunosuppressed patients, including those with HIV infection, may have «atypical» findings on chest radiography — e. g., lower-zone infiltrates without cavity formation.

The evaluation of patient with tuberculosis includes all the pointes of a routine examination of a person with any respiratory disease.

Systemic symptoms and signs of tuberculosis

Although systemic signs and symptoms are classically ascribed to TB in medical textbooks, and are indeed very important for diagnostic suspicion, it should be kept in mind that they are nonspecific and can be present in other diseases of insidious evolution, particularly other bacterial and mycotic bronchopulmonary infections, lung cancer, and chronic diseases with lung involvement.

Fever and sweating

It is believed that bacillary multiplication increases in the afternoon, with the daily circadian rhythm cortisol peak, which is followed by the evening fever

characteristic of the disease. M. tuberculosis multiplies at a slow pace in comparison with other bacteria and therefore the inflammatory process is moderate and is accompanied by a low-grade fever. The body responds to the evening fever with night sweats to maintain the body temperature. However, when there is massive hematogenous or endobronchial dissemination, peaks of high fever can occur at any time of the day and are accompanied by chills.

Weight loss

Consumption was the name given to TB many years ago because it appeared to consume those affected, and anorexia and weight loss are still frequent in TB patients (about 70 % of the cases). Weight loss is proportional to the duration and extent of the disease and is frequently accompanied by adynamia.

Respiratory symptoms and signs of pulmonary tuberculosis

Cough

Cough is present in virtually all patients with pulmonary TB. Cough results from the stimulus caused by the alveolar inflammatory process or from the granulomatous impingement into the respiratory airways. At the onset of the disease, the cough is dry; but with progression, it becomes productive with mucous or mucopurulent expectoration, generally in small amounts, and sometimes with blood. Cough is less frequent in the pleural form of the disease. It is worth mentioning that cough tends to be ignored or minimized by smokers, who may have a chronic cough, so questions about changes in the usual pattern can be of great value in increasing suspicion of pulmonary TB.

Hemoptysis

When hemoptysis occurs, the blood volume is variable, from bloody streaks mixed in the sputum (hemoptoic sputum) to massive hemoptysis (more than 400 mL/day), which is rare. A higher volume of hemoptysis is generally caused by erosion of Rasmussen's aneurysms, which are free terminations of arteries within lung cavities. Bleeding can also occur in small lesions during the formation of the cavities, when hemoptysis can be the first manifestation of the disease, which was known by the old phthysiologists as alert hemoptysis or bark.

Dyspnea

Although the inflammatory process of TB causes global parenchyma destruction of both alveoli and blood vessels, there is no gross alteration in the ventilation/perfusion ratio, except in cases of atelectasis, large cavities or lesions with a large acute inflammatory infiltration. Therefore, dyspnea is not a common symptom, but can be caused by pleural effusions, pneumothorax or restriction caused by fibrosis in advanced disease. Dyspnea may be more frequent in the miliary form, due to diffuse interstitial disease and consequent hypoxemia. An obstructive pattern of airway disease can result from the bronchial hyperresponsitivity that often accompanies TB and its sequelae.

Thoracic pain

Thoracic pain occurs when there is pleural involvement, but as the TB pathological process begins in the alveoli, very close to the pleural surface, this

is an early and relatively frequent symptom. Generally of low intensity, it disappears within two or three weeks after effective treatment has begun.

Hoarseness

This occurs when the larynx is affected, which is frequent with pulmonary TB. It rarely occurs in other forms of the disease. When cough and other symptoms are overlooked by the patient, hoarseness may be the sole reason for seeking medical assistance.

Physical examination

Physical signs in TB are related to the extent of the lesions, the duration of the disease and the form of presentation. The longer the duration of the disease, the more evident are the classic signs of consumption, such as pallor and weight loss. The extent and the form of the disease in the lung parenchyma determine the presence of specific pulmonary signs.

The most common auscultation findings are:

- coarse crackles in the area corresponding to the lesion (generally apical and posterior);
- wheezing and ronchi in the area of compromised bronchi; clinical signs of lung condensation in the forms with caseous pneumonia;
- decreased vesicular murmur and broncophony or tubular blow when pleural effusion is present;
- as well as the classic amphoric breath sounds near cavities.

Hepatosplenomegaly can occur in the disseminated forms.

Some findings are caused by delayed-type hypersensitivity to tubercle bacilli components, although the lesions themselves do not contain M. tuberculosis.

These TB associated conditions are:

- erythema nodosum (inflammation of the subcutaneous adipose tissue),
- phlyctenular conjunctivitis,
- erythema induratum of Bazin (nodular vasculitis)
- polyserositis.

These lesions are mostly associated with primary TB infection, although they may also be observed in re-activation TB disease and sometimes are recurrent.

Table 2.1 — TB symptoms

Respiratory symptoms	General symptoms (tuberculous intoxication)
+++Cough	++Loss of weight
+++Sputum	++Fever and sweating
++Hemoptysis	+Tiredness
+Chest wall pain	+Loss of appetite
+Breathlessnes	
+Localized wheeze	
+Frequent colds	
The number of plus (+) shows which symptoms are most important	
Note that all the symptoms could be due to other illnesses. To make sure, you must examine the sputum for TB	

One of the most important signs, which should make to think of possible tuberculosis, is that the symptoms have come on gradually over weeks or months. This applies particularly to the general symptoms of illness: loss of weight, loss of appetite, tiredness or fever.

2.2. Radiographic procedures in diagnosis (chest radiography, computer tomography, magnetic resonance imaging). Certain radiographic abnormalities are consistent with tuberculosis

Chest X-ray in diagnosis

Pulmonary tuberculosis in adults can present with a wide variety of radiographic features. Chest radiography is not a method of diagnosis. When it is available, it can be used to screen patients with respiratory symptoms to identify features that might be caused by tuberculosis, or that are consistent with other diseases, or to demonstrate the absence of abnormality.

Indications for CXR

Positive sputum smear

The first screening test for PTB suspects is sputum smear microscopy. In most cases of sputum smear-positive PTB a CXR is not necessary. In a few cases, a CXR may be necessary; the indications are as follows:

a) suspected complications in a breathless patient, needing specific treatment, e.g. pneumothorax, pericardial effusion or pleural effusion (note that a positive sputum smear is rare in pericardial effusion and pleural effusion);

b) frequent or severe haemoptysis (to exclude bronchiectasis or aspergilloma);

c) only 1 sputum smear positive out of 3 (in this case, an abnormalCXR is a necessary additional criterion for the diagnosis of sputum smear-positive PTB).

Negative sputum smear

Reassess patients who continue to cough despite a course of broad-spectrum antibiotic, and who have had at least two (and preferably three) negative sputum smears. If you still suspect TB despite negative sputum smears, the patient needs a CXR.

A few principles can aid student in viewing films

First, the appearance of any structure on a radiograph depends on the structure’s density; the denser the structure, the whiter it appears on the fi lm. At one extreme is air, which is radiolucent and appears black on the fi lm. At the other extreme are metallic densities, which appear white. In between is a spectrum of increasing density from fat to water to bone. The viscera and muscles fall within the realm of water density tissues and cannot be distinguished in radiographic density from water or blood.

Second, in order for a line or an interface to appear between two adjacent structures on a radiograph, the two structures must differ in density. For example, within the cardiac shadow the heart muscle cannot be distinguished from the blood coursing within the chambers because both are of water density.

In contrast, the borders of the heart are visible against the lungs, because the water density of the heart contrasts with the density of the lungs, which is closer to that of air. However, if the lung adjacent to a normally denser structure (e.g., heart or diaphragm) is airless, either because of collapse or consolidation, the neighboring structures are now both of the same density, and no visible interface or boundary separates them. This principle is the basis of the useful *silhouette sign.* If an expected border with an area of lung is not visualized or is not distinct, the adjacent lung is abnormal and lacks full aeration.

Chest radiographs usually are taken in two standard views—posteroanterior (PA) and lateral. Knowledge of radiographic anatomy is fundamental for interpretation of consolidation or collapse (atelectasis) and for localization of other abnormalities on the chest film. Lobar anatomy and the locations of fissures separating the lobes are shown in Figure 2.1.

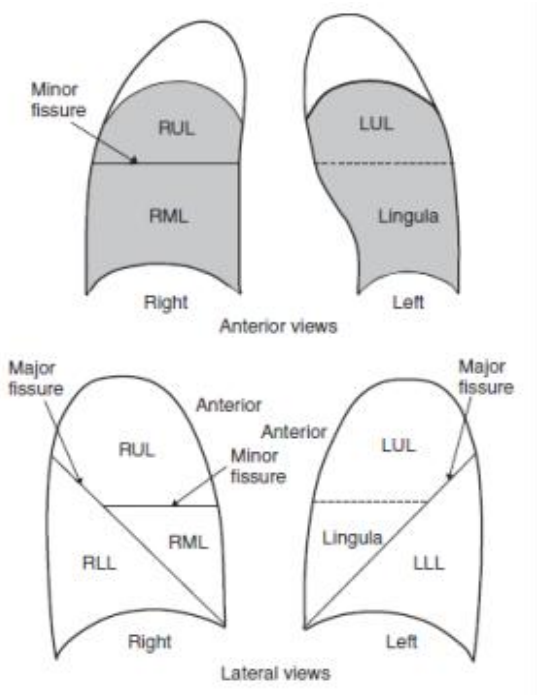


Figure 2.1 — Lobar anatomy as seen from anterior and lateral views. In anterior views, *shaded regions* represent lower lobes and are behind upper and middle lobes. Lingula is part of the left upper lobe; *dashed line* between the two does not represent a fissure. LLL — Left lower lobe;LUL — left upper lobe; RLL — right lower lobe; RML — right middle lobe; RUL — right upper lobe.

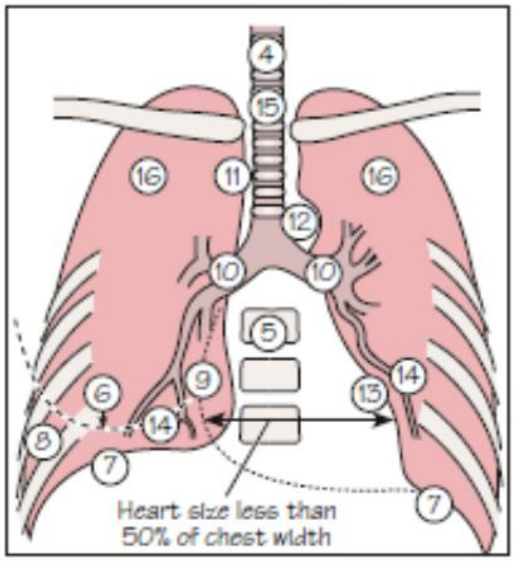
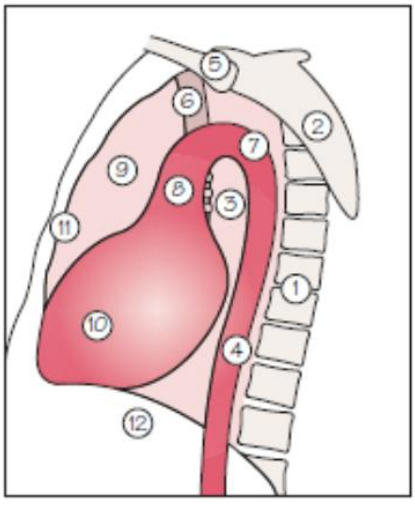
Certain radiographic abnormalities are consistent with tuberculosis:

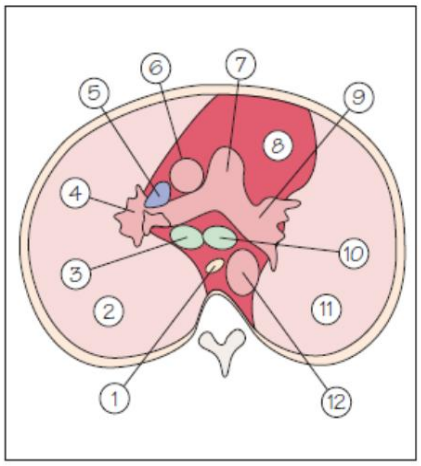
• Nodules are round shadows (or «densities») with clearly defined borders; their size varies from a micronodule (less than 3mm in diameter), to a nodule (more than 3 mm and less than 1 cm in diameter), to a round shadow (more than 1 cm in diameter);

• Patchy shadows, or infiltrations, have irregular borders that are not as clearly defined. They are of varying size, sometimes extending to large parts of the lungs.

• Cavities are the most characteristic sign of tuberculosis. A cavity is an area of lucency with a fairly thick wall (more than 1mm), in which an area of bronchial drainage, demonstrated by opaque parallel lines, may be evident at the pole closest to the hilum of the lung. Cavities sometimes contain liquid at the base (liquefied caseous material), evident as an «air fluid level».

Table 2.2 — Chest radiograph interpretation

Evaluation of the CXR includes all the following: 1. Date: 2. Name 3. AP/PA: Is it AP (anteroposterior) or PA (posteroanterior)? (Heart size cannot be measured if AP) 4. Is it well positioned? The trachea should be midway between clavicles 5. Penetration: The disc spaces should be just visible through the cardiac shadows (underpenetrated = plethoric lungs overpenetrated = dark lungs) 6. Soft tissues and breast shadows (mastectomy in a female) 7. Right diaphragm 2 cm higher than left (raised when paralysed, flat in asthma/COPD) 8. Check ribs for fractures, metastases 9. Right heart border = right atrium 10. Hilium = bronchi, arteries and veins 11. Superior vena cava 12. Aortic arch 13. Left heart border = left ventricle 14. Pulmonary vessels 15. Trachea and main bronchi 16. Lung fields	
1. Thoracic vertebral bodies 2. Scapula 3. Pulmonary trunk and hilium 4. Descending aorta 5. Head of clavicle 6. Trachea 7. Arch of aorta 8. Ascending aorta 9. Anterior space (thymus) 10. Heart 11. Sternum 12. Diaphragm	

1. Oesophagus 2. Right lung 3. Right main bronchus 4. Right pulmonary artery and branches 5. Superior vena cava 6. Ascending aorta 7. Pulmonary trunk 8. Mediastinum and heart 9. Left pulmonary artery and branches 10. Left main bronchus 11. Left lung 12. Descending aorta	

In tuberculosis, a wide variety of abnormalities may be present on the same film. In films taken at least 2 weeks apart, changes in the abnormalities can be detected: growth of the cavities, confluence and spread of the nodules, or the formation of a cavity inside a patchy shadow. This kind of evolution of the radiographic features suggests that the tuberculosis is clinically active.

When the tuberculosis has progressed over several months, the destruction of the lung parenchyma and gradual fibrosis lead to retraction of the neighbouring structures: the trachea may be displaced, the hilum may become elevated, the diaphragm may be pulled upward and the cardiac silhouette may change shape and place.

Lesions due to tuberculosis can be unilateral or bilateral; they are most frequently observed in the upper zones of the radiograph. The extent of the abnormalities may vary from a minimal lesion (an area less than the size of a single intercostal space), to far advanced lesions, with extensive involvement of both lungs.

Some radiographs show tuberculosis sequelae

Pulmonary tuberculosis lesions may have various types of sequelae:

• nodules that are fully or partially calcified
• stellate abnormalities
• fibrous retraction
• fine-walled bullae/cavities

In some cases the retraction may be extensive, and may affect a whole lobe or even a whole lung.

2.3. Bacteriological diagnostics. Induced sputum. Sputum smear microscopy and culture. Ziehl-Neelsen staining and AFB microscopy. Fluorescent auramine staining. Classic method of cultivation onLöwenstein-Jensen media. Automated culture methods.Genotypic methods of MBT identification and drug resistance detection

The principal method of pulmonary TB diagnosis is microscopic examination of Ziehl-Neelsen stained sputum samples for AFB. For bacteriological examination, the quality of the samples sent to the laboratory is of fundamental importance.

For pulmonary tuberculosis: the specimen that should be collected for examination is sputum obtained from the patient after coughing (more rarely the sample is obtained by gastric aspiration or bronchoscopy). As sputum can be contaminated by other bacteria, it must be collected in clean sputum containers (non-sterile) that can be firmly sealed. All sputum samples that are not examined at the center where they are collected must be stored and transported following strict guidelines.

For extrapulmonary tuberculosis: fluid from serous effusion, cerebrospinal fluid (CSF) or biopsied fragments can be sent to the laboratory for culture. All sampling must be performed in strictly sterile conditions so that culture can be performed directly without prior decontamination. Samples must never be placed in formol, which kills the bacilli.

Induced sputum

When the patient does not produce expectorant, it is advisable to induce sputum by nebulization with hypertonic (3 to 5 %) saline solution. Recent studies showed that induced sputum has a diagnostic yield equal to or higher than that of material collected by fiberoptic bronchoscopy. When miliary TB is suspected but the smears are negative for AFB, fiberoptic bronchoscopy with bronchial biopsy is recommended for a definitive diagnosis.

Sputum smear microscopy and culture

AFB Microscopy

There are several staining methods used for the tubercle bacillus; it is important for the method or methods used to be standardized for each country. The stains that are the most effective are hot Ziehl-Neelsen (ZN) staining and auramine staining.

Ziehl-Neelsen staining

The smear is covered with carbol fuchsin, and then heated. The smear is then destained successively using sulfuric acid and alcohol. All of the smears must be almost totally destained, and then restained with methylene blue. The bacilli are stained red by the fuchsin and are resistant to the acid and alcohol, hence the name **acid-fast bacilli (AFB).**

Destaining by the successive application of acid and alcohol can also be done using only 25 % sulfuric acid; however, it should be applied several times until the smear is completely destained.

On microscopic examination of the stained smear, the tubercle bacilli look like fine, red, slightly curved rods that are more or less granular, isolated, in pairs or in groups, and stand out clearly against the blue background.

The stained smear is examined using a binocular microscope with an immersion lens (magnification × 100). The number of AFB per 100 fields (about one length and one width of a slide) are counted. This technique is simple, rapid and fairly inexpensive.

Fluorescent auramine staining

The fuchsin is replaced by auramine; the bacilli fix the fluorescent stain and retain it after the acid and alcohol staining.

The stained smear is examined by fluorescence microscopy with a dry lens of low magnification (*25 or 40). This microscope has an ultraviolet lamp to enable the fluorescent bacilli to be seen: they are clearly visible in the form of greenish-yellow fluorescent rods.

The sensitivity and specificity of examination by fluorescence microscopy are comparable to those of microscopy after ZN staining. The main advantage is the ease and rapidity of reading: on the same slide surface, the results of 10 minutes' reading by optic microscope are obtained in 2 minutes on fluorescence microscopy.

As this technique requires more costly equipment (the microscope itself, and the lamps, which need to be replaced frequently — on average after 200 hours of use), it is cost-effective only if more than 30 slides are examined each day. A constant electricity supply and trained technicians are also indispensable.

Record the results

The number of bacilli present in a patient's sputum is in direct relation to the degree of infectiousness. For this reason the result must be recorded in a quantitative fashion.

Table 2.3 — Reading method for smears stained by Ziehl-Neelsen

Number of bacilli	Result reported	
0	AFB per 100 oil immersion fields	0
1–9	AFB per 100 oil immersion fields	exact number of AFB
10–99	AFB per 100 oil immersion fields	+ (1+)
1–10	AFB per oil immersion fields	++ (2+)
>10	AFB per oil immersion fields	+++ (3+)

Sputum smear microscopy for tubercle bacilli is positive when there are at least 10000 organisms present per ml of sputum. Such a high number of bacilli is found only in the lesions of patients with cavitary pulmonary tuberculosis.

Classic culture methods

When M. tuberculosis is cultured from clinical specimens (e. g. sputum, lymph node aspirate, cerebrospinal fluid) this provides the gold standard for the definitive diagnosis of TB. Tubercle bacilli that have grown in culture can also be tested in vitro for sensitivity to anti-TB drugs. The usual culture medium is Löwenstein-Jensen, although liquid culture media and automated systems (e. g. Bactec) can also be used in more sophisticated laboratories.

Most pathological specimens, except those that are obtained from closed lesions (serous membranes, joints, samples obtained from surgery), are contaminated by other bacteria. In order to destroy these bacteria, which can contaminate the culture media; it is important to decontaminate the sample with basic antiseptics, which kill the contaminants much more rapidly than the mycobacteria. Decontamination also homogenizes the specimen.

The specimens are then centrifuged, the supernatant is discarded and the sediment is neutralized using a mild acid.

The centrifuged sediment is inoculated into at least two tubes containing a specific culture medium, usually Löwenstein-Jensen medium (a solid egg-enriched medium).

The inoculated tubes are placed in an incubator at 37 °C for 4–12 weeks. As tuberculous mycobacteria grow very slowly (an average period of doubling of 13–20 hours), colonies will be visible to the naked eye after at least 3 weeks' incubation.

When growth has occurred on culture, large, rounded, buff-coloured "cauliflowerlike" colonies are visible to the naked eye on the surface of the culture medium; they have a dry, rough surface, and are isolated or confluent, depending on the number of bacilli present in the original sample.

When colonies appear, they must be identified according to criteria based on their macroscopic aspect (rough colonies) and by their response to biochemical tests: M.tuberculosis colonies have a thermolabile catalase activity (positive at 22 °C, destroyed by heat at 68 °C), and a nitrate reductase activity, and they accumulate nicotinic acid or niacin, which can be demonstrated by the niacin test. In other cases another mycobacterium must be identified (M. bovis, BCG or atypical mycobacteria).

The number of colonies present in the culture tubes is in direct relation to the number of bacilli in the lesions. This is why the colonies are counted and the results are expressed as the number of colonies per tube, except if their number is so high that they are confluent (in this case the result will be expressed as innumerable confluent colonies).

Other culture methods (Automated culture methods)

Growth in the liquid media is faster than that in solid media, and automated commercial broth systems allow for growth detection within 1–3 weeks compared with solid media, where growth takes 3–8 weeks.

The BACTEC TB-460 system was the first, and for many years the only, automated approach in mycobacteriology. It makes use of a radiometric instrumentation developed for blood cultures with the broth bottles replaced by vials containing a medium specific for mycobacteria. A modified Middlebrook 7H9 medium is used, in which one of the components, palmitic acid, is radiolabeled with ^{14}C. Contamination is controlled bynthe addition, prior to use, of a mixture of polymyxin B, amphotericin B, nalidixicn acid, trimethoprim and azlocillin (PANTA) reconstituted with a poly-oxyethylene solution. When viable mycobacteria are present in the culture vial, the radiolabeled palmitic acid is metabolized and radioactive CO2 is liberated into the gaseous phase. The reading is usually performed twice a week during the first 15 days of incubation, and weekly thereafter, until the 42nd day.

The BACTEC MGIT 960 system uses the technology of the previously developed blood culture instrument. Mycobacteria Growth Indicator Tube (MGIT) is a modified Middlebrook 7H9 medium in which a supplement is added at the moment of use. The supplement is a mixture of oleic acid, albumin, dextrose, and catalase (OADC) enrichment and the same PANTA antibiotic mixture used in the radiometric system. If viable mycobacteria are present in the tube, oxygen is consumed due to their metabolism, the quenching effect lowers accordingly, and the bottom of the tube fluoresces when exposed to ultraviolet light.

The BACTEC MGIT960 is a typical walk-away instrumentation which monitors the tubes at one-hour intervals, alerts when they become positive and signals the end of the incubation period.

Molecular genetics or PCR

To detect *M. tuberculosis* a multitude of nucleotide sequences of a single copy of a target sequence of the bacillus can be obtained in a few hours using a genome amplification technique. Specific probes are then used to identify the different mycobacteria. This technique is known as the polymerase chain reaction (PCR).

PCR can detect and identify the presence of M. tuberculosis in a pathological specimen within 24 to 48 hours. However, it is of less sensitivity compared with culture (80 % on average), and its specificity is from 97–98 %. This delicate technique, which requires sophisticated, costly equipment, is limited to research.

Genotypic methods to Diagnose M(X)DR TB

Genotypic methods look for genetic determinants of resistance rather than the resistance phenotype and have the advantage of a shorter turnaround time.

They are:

- ***PCR Sequencing***

Sequencing is the gold standard method for mutation detection. It is accurate and reliable and has been widely used for characterizing mutations in the rpoB gene in rifampicin-resistant strains and to detect mutations responsible for resistance to other anti-tuberculosis drugs.

- ***Solid-phase Hybridization Techniques***

✓ the Line Probe Assay (INNO-LiPA) for the detection of rifampicin resistance

✓ GenoType MTBDR assay (Hain's test) for the simultaneous detection of isoniazid and rifampicin resistance based on the detection of the most common mutations in the katG and rpoB genes respectively.

- ***Real-time PCR Techniques***.

Real-time PCR techniques (GeneXpert ® MTB/R) have also been introduced for rapid detection of drug resistance using different probes. The main advantages of real-time PCR techniques are the speed of the test and a lower risk of contamination.

MYCOResist (PCR-Sequencing)

Among the different genotypic tests PCR Sequencing is considered as 'gold standard' for nucleic acid identification and mutation detection; however it needs expertise and sequencing facilities. DNA Sequencing offers benefit of screening both known as well as novel mutations.

Advantages:

- High sensitivity (97 %), specificity (100 %) and is also rapid, as compared to culture based methods.
- Detects:

✓ mutations in codon of katG gene indicating resistance to Isoniazide;

✓ mutations in codons of rpoB gene indicating resistance to Rifampicin.

Line Probe Assay (INNO-LiPA) is based on reverse hybridization of amplified DNA from cultured strains or clinical samples to ten probes covering the core region of the rpoB gene of M. tuberculosis, immobilized on a nitrocellulose strip. From the pattern of hybridization obtained, the presence or absence of mutated or wild regions is visualized by a colorimetric reaction and the strain can be considered as resistant or susceptible to Rifampicin.

Advantages:

- High sensitivity (97 %), specificity (100 %).
- Allows rapid detection of resistance to RIF directly fromsputum samples.

The GenoType MTBDR plus is based on the DNA-Strip technology and permits the simultaneous molecular genetic identification of

✓ the M. tuberculosis complex;

✓ its resistance to rifampicin and isoniazid by the detection of the most common mutations in the rpoB gene, katG gene and inhA gene from smear-positive pulmonary clinical specimens or cultivated samples.

Advantages:

- Results are obtained in 4–5 hrs only.
- Combination of specific amplification and hybridization guarantees diagnostic reliability, high sensitivity and specificity (sensitivity of 88.,9 % for MDRTB detection, with a specificity of 100 %).
- Also due to inclusion of inhA gene, it helps in detection of low level of isoniazid resistance

GenoType MTBDRsl-FQ, Am, Ethambutol (Hains Test) is based on the DNA-Strip technology and permits the simultaneous molecular genetic identification of the:

✓ M. tuberculosis complex;

✓ its resistance to fluoroquinolones like ofloxacin and moxifloxacin by the detection of the most common mutations in the gyrA gene;

✓ its resistance to the injectable antibiotics (viomycin, kanamycin, amikacin and capreomycin) by detection of the most common mutations in the rrs-gene;

✓ its resistance to the first-line drug ethambutol by detection of the most common mutations in the embB gene from smear-positive pulmonary clinical specimens or cultivated samples.

Advantages:

- Detection of XDR-TB in patients previously diagnosed with MDR-TB.
- Confirmation of DST results.
- Results are obtained in 4–5 hrs only.
- High sensitivity, specificity and diagnostic reliability

GeneXpert®MTB/RIF

The rapid and fully automated Xpert®MTB/RIF test is a TB-specific real time cartridge-based automated DNA amplification test. It is highly sensitive for

confirmation of both smear positive and smear negative samples. Assay targets the rpoB gene, which is critical for identifying mutations associated with rifampicin resistance.

Advantages:

- Deliver a highly accurate result in less than 2 hours.
- Simultaneous detection of both MTB and rifampicin resistance, a marker for MDR strains, as up to 95 % of rifampicin resistance strains are INH resistance.
- Unprecedented sensitivity for detecting MTB even in smear negative, culture positive specimens

The Xpert® MTB/RIF cannot be used for treatment monitoring, as it detects both live and dead bacteria. Microscopy culture and drug sensitivity testing are still required to monitor treatment progress and to detect other types of drug resistance. The main advantages of the test are, for diagnosis, reliability when compared to sputum microscopy and the speed of getting the result when compared with culture. For diagnosis of TB, although sputum microscopy is both quick and cheap, it is often unreliable. Although culture gives a definitive diagnosis, to get the result usually takes weeks rather than the hours of the Xpert test. The main advantage in respect of identifying rifampicin resistance is again the matter of speed. The cost of the test and high technical requirements are the disadvantages.

Benefits of Genotypic Methods

Culture sensitivity remains the «gold standard» for screening of MDR-TB. However, Lowenstein Jensen method is highly time consuming (6–8 weeks). Radiometric methods such as BACTEC 460 have enabled to reduce the detection time to 2 weeks, and non-radiometric fully automated systems require 7 to 10 days, beginning from the time that a positive culture is obtained.

Phenotypic methods do not satisfy the requirement of rapid and sensitive results. Thus, genotypic methods for screening of mutations responsible for drug resistance forms a better alternative before starting the treatment empirically

Table 2.4 — Genotypic Tests

Test Name	Sample
MYCOResist (PCR-Sequencing)	Sputum/CSF/BAL/pleural fluids/urine/culture (specimens of patients with AFB smear less than 1+ are not acceptable) + clinical history
Line Probe Assay (INNO-LiPA)	Sputum (AFB Smear Positive)/BAL (AFB Smear Positive) / MTB Culture Specimen
MDR-TB rapid genotypic test (H,R)	Sputum (AFB Smear Positive)/BAL (AFB Smear Positive) / MTB Culture Specimen
Genotypic assay — anty-TB second line drug (Fq, Am, E)	Sputum (AFB Smear Positive)/BAL (AFB Smear Positive) / MTB Culture Specimen
GeneXpert® MTB/RIF	Sputum or BAL (Storage at maximum 35 °C for < 3days and at 4 °C for 4–10 days.)

Early suspicion of drug-resistance and drug susceptibility testing is necessary to thwart the menace of MDR-TB.

Drug Susceptibility testing

In general, the initial isolate of *M.tuberculosis* should be tested for susceptibility to isoniazid, rifampin, and ethambutol. In addition, expanded susceptibility testing is mandatory when resistance to one or more of these drugs is found or the patient either fails to respond to initial therapy or has a relapse after the completion of treatment. Susceptibility testing may be conducted directly (with the clinical specimen) or indirectly (with mycobacterial cultures) on solid or liquid medium. Results are obtained most rapidly by direct susceptibility testing on liquid medium, with an average reporting time of 3 weeks. With indirect testing on solid medium, results may be unavailable for 8 weeks. Molecular methods for the rapid identification of genetic mutations known to be associated with resistance to rifampin and isoniazid have been developed

Susceptibility tests are used to determine the susceptibility or resistance of a patient's bacillary strain to the different anti-tuberculosis drugs. These tests are delicate because of the presence of resistant mutant bacilli in the susceptible strains. In a wild susceptible bacillary strain (which has never been in contact with anti-tuberculosis drugs) from a case with cavitary pulmonary tuberculosis, the majority of bacilli are susceptible, but some rare bacilli are resistant to the different anti-tuberculosis drugs: these are resistant mutants. These bacilli appear in a susceptible strain, without having been in contact with an antituberculosis drug, because of chromosomal mutation as soon as the bacillary population is very large. The pulmonary cavities are the only tuberculosis lesions that are sufficiently rich in bacilli for these mutations to occur.

This phenomenon of mutation is:

- Spontaneous: mutation occurs in a bacillary strain without the strain's having come into contact with anti-tuberculosis drugs.
- Rare and specific: in a population of 108 bacilli, the probability of finding resistant bacilli varies depending on the anti-tuberculosis drug: a single mutant resistant to rifampicin, 103 to isoniazid, 103 to streptomycin, 104 to pyrazinamide.
- Hereditary: this mutation is transmitted to all the bacilli that result from the multiplication of the resistant mutant.

On the other hand, when a strain is resistant to an anti-tuberculosis drug, most of the bacilli are resistant to this drug, and the rest of the strain is composed of susceptible bacilli and some mutants resistant to the other drugs.

Therefore, when a patient presents with a strain that is resistant to an antituberculosis drug, the whole bacillary population will contain a very high proportion of resistant bacilli. To determine the resistance of a strain to antituberculosis drugs, the classic method used is the «proportion method», based on the determination of a sufficiently high proportion of colonies of resistant bacilli in the entire bacillary population, in order to confirm the resistance of the strain.

There are two types of susceptibility testing:

• indirect susceptibility testing, performed after obtaining colonies in culture before testing; the results are available only 2 to 3 months after sampling.

• direct susceptibility testing, performed directly on the sample if it is rich in bacilli (i.e. if the smear made from the sample is strongly positive). In this case the results are available in 4–6 weeks.

These tests should be performed only in laboratories where this delicate technique is commonly used and where internal and external quality controls are conducted to confirm its reliability.

Susceptibility testing is unnecessary in the treatment of the majority of patients, except in certain individual cases. Its main role is in the conduct of nationwide studies in the epidemiological surveillance of tuberculosis.

Phenotypic testing in the laboratory

Minimum inhibitory concentrationis the lowest concentration of an antimicrobial that will inhibit the visible growth of a microorganism. Visibility of growth starts at 5×10^5 cells/ml. It was found that drug-susceptible strains of M. tuberculosis that have not been exposed to anti-TB drugs (wild-type strains) do not exhibit much variation in minimum inhibitory concentration to those drugs.

C*ritical concentration* is defined as drug concentration that inhibits the growth of wild-type strains, without appreciably affecting the growth of strains with alterations in drug susceptibility. This categorizes a clinical M. tuberculosis isolate as either susceptible or resistant.

2.4. Tuberculin skin test. Value of a positive and negative result. False-positive reactions. TST suppressing factors. IFN-γ Release Assays (IGRAs). Diaskin-test

Tuberculin Skin Test

Tuberculin is a purified protein derived from tubercle bacilli. Another name for tuberculin is PPD (purified protein derivative). Following infection with M. tuberculosis, a person develops hypersensitivity to tuberculin. Tuberculin injected into the skin of an infected person produces a delayed local reaction after 24–48 hours. This reaction is quantified by measuring the diameter of skin induration (thickening) at the site of the reaction. Various conditions can suppress this reaction. The reaction indicates hypersensitivity. In other words, the reaction only shows that the person has at some time be infected with M. tuberculosis. False-positive reactions may be caused by infections with nontuberculous mycobacteria and by bacille Calmette-Guérin (BCG) vaccination.

The standard amount of tuberculin used is 5 units, injected as 0,1 ml into the anterior surface of the forearm at the junction of the middle and upper thirds. It is very important that the tuberculin is injected intradermally so that it is well localized. If correctly given, the injection should raise a small bump of 5 mm or more in diameter, which disappears within 1–2 hours.

Value of a negative tuberculin test

A tuberculin test is not significant, or «negative», when the diameter of skin induration is less than 10 mm (or less than 5 mm in an HIV-infected patients). A negative tuberculin skin test does not exclude TB. Thus, it is of no

help in deciding that someone does not have TB. The table below shows the conditions that can suppress a tuberculin skin test in a person with active TB.

Conditions that may suppress the tuberculin skin test:

- HIV infection;
- malnutrition;
- severe bacterial infections, including TB itself;
- viral infections, e.g. measles, chickenpox, glandular fever;
- cancer;
- immunosuppressive drugs, e. g. steroids;
- incorrect injection of PPD.

Value of a positive tuberculin skin test

The criterion for a significant or «positive» tuberculin test depends on whether a child has previously had BCG vaccination or not. This is because a reaction to tuberculin is usual after a previous BCG, at least for several years. The reaction is usually weaker (diameter often less than 10 mm) than the reaction to natural infection with M. tuberculosis. A tuberculin test is considered significant or positive when the diameter of skin induration is 10 mm or more. However, if the child is HIV-infected, the tuberculin test is considered positive if the induration is 5 mm or more. A positive tuberculin test is only one piece of evidence in favour of the diagnosis of TB. The younger the child and the greater the diameter of induration, the stronger is that one piece of evidence.

IFN-γ Release Assays (IGRAs)

Recently, two in vitro assays that measure T-cell release of IFN- γin response to stimulation with the highly tuberculosis-specific antigens. IGRAs are more specific than the TST as a result of less cross-reactivity due to BCG vaccination and sensitization by nontuberculous mycobacteria. IGRAs also appear to be at least as sensitive as the TST for active tuberculosis (used as a surrogate for LTBI). Although diagnostic sensitivity for LTBI cannot be directly estimated because of the absence of a gold standard, these tests have shown better correlation than the TST with exposure to M. tuberculosis in contact investigations in low-incidence settings.

Other potential advantages of IGRAs include logistical convenience, the need for fewer patient visits to complete testing, the avoidance of unreliable and somewhat subjective measurements such as skin induration, and the ability to perform serial testing without inducing the boosting phenomenon (a spurious TST conversion due to boosting of reactivity on subsequent TSTs among BCG-vaccinated persons and those infected with other mycobacteria). Because of the high specificity and other potential advantages, IGRAs are likely to replace the TST for LTBI diagnosis in low-incidence, high-income settings where cross-reactivity due to BCG might adversely impact the interpretation and utility of the TST.

Serologic and Other Diagnostic Tests for Active Tuberculosis

A number of serologic tests based on detection of antibodies to a variety of mycobacterial antigens are marketed in some countries. Careful independent assessments of these tests suggest that they are not useful as diagnostic aids, espe-

cially in persons with a low probability of tuberculosis. Various methods aimed at detection of mycobacterial antigens in diagnostic specimens are being investigated but are limited at present by low sensitivity. Determination of ADA levels in pleural fluid may be useful in the diagnosis of pleural tuberculosis; the utility of this test in the diagnosis of other forms of extrapulmonary tuberculosis (e. g., pericardial, peritoneal, and meningeal) is less clear.

Additional Diagnostic Procedures

Other diagnostic tests may be used when pulmonary tuberculosis is suspected. Sputum induction by ultrasonic nebulization of hypertonic saline may be useful for patients who cannot produce a sputum specimen spontaneously. Frequently, patients with radiographic abnormalities that are consistent with other diagnoses (e. g., bronchogenic carcinoma) undergo fiberoptic bronchoscopy with bronchial brushings and endobronchial or transbronchial biopsy of the lesion. Bronchoalveolar lavage of a lung segment containing an abnormality may also be performed. In all cases, it is essential that specimens be submitted for AFB smear and mycobacterial culture. For the diagnosis of primary pulmonary tuberculosis in children, who often do not expectorate sputum, specimens from early-morning gastric lavage may yield positive cultures.

Table 2.4 — Current methods of tuberculosis diagnosis

Method	Advantages	Disadvantages
Clinical signs	Rapid diagnosis	Not specific, not conclusive Not always present
X-Ray	Readily available	Not specific or conclusive
Microscopy (smear for acid-fast bacilli)	Low cost Rapid diagnosis	Low sensitivity (up to 2/3 of pulmonary TB cases are negative) Difficult sample collection
Culture	Specific	Time consuming (up to 4–8 weeks) Not always possible
PCR	Relatively quick Very specific	Relatively expensive High level of training required Expensive instrumentation Can detect latent disease

3. CLASSIFICATION OF TUBERCULOSIS. TUBERCULOSIS IN CHILDREN. DISSEMINATED AND MILIARY TB

3.1. Clinical forms of tuberculosis. Signs and criterions of active TB disease Classification

- primary pulmonary tuberculosis;
- acute disseminated tuberculosis: meningitis and miliary tuberculosis;
- post-primary pulmonary tuberculosis;
- extrapulmonary tuberculosis.

Table 3.1 — TB classification (primary TB)

Primary tuberculosis	no clinical disease positive tuberculin skin test (usual outcome: 90 % of cases)
	hypersensitivity reactions e. g. erythema nodosum phlyctenular conjunctivitis dactylitis
	pulmonary, mediastinal lymph nodes and pleural complications e. g. primary complex isolated mediastinal lymphadenopathy mediastinal lymphadenopathy with hyperinflation and collapse/consolidation pleural effusion
	disseminated disease lymphadenopathy (usually cervical) meningitis pericarditis miliary disease

Table 3.2 — TB classification (Post-primary tuberculosis)

Pulmonary TB	
cavities upper lobe infiltrates fibrosis progressive pneumonia endobronchial	
Extrapulmonary TB	
Common Pleural effusion Lymphadenopathy (usually cervical) Central nervous system (meningitis, cerebral tuberculoma) Pericarditis (effusion/constrictive) Gastrointestinal (ileocaecal, peritoneal) Spine, other bone and joint	***Less common*** Empyema Male genital tract (epididymitis, orchitis) Female genital tract (tubo-ovarian, endometrium) Kidney Adrenal gland Skin (lupus vulgaris, tuberculids, miliary)

Clinical classification of tuberculosis in Belarus

The classification consists of four basic sections:

1. Clinical forms of tuberculosis.
2. Characteristic of tubercular process.
3. Complication of tuberculosis.
4. Residual changes after the cured tuberculosis.

A. Main clinical forms

The clinical forms of tuberculosis differ on localization and clinical and X-ray features, with the consideration of pathogenic and pathomorphologic characteristics of the tubercular process.

Pulmonary tuberculosis

Primary tubercular complex;
Intrathoracic lymphatic nodes tuberculosis
Disseminated tuberculosis;
Miliary tuberculosis;
Focus pulmonary tuberculosis;
Infiltrative tuberculosis;
Caseous pneumonia;
Tuberculoma;
Cavernouse tuberculosis;
Fibrotic-cavernouse lung tuberculosis;
Cirrhotic tuberculosis;
Tuberculosis pleurisies (including empyema);
Tuberculosis of upper respiratory tract;
Respiration organs tuberculosis combined with professional lung diseases (Coniotuberculosis).

Nonpulmonary tuberculosis (Tuberculosis of other organs and systems)

Tuberculous meningitis, of central nervous system
Tuberculosis of intestines, peritoneum, mesentery lymphatic nodes
Tuberculosis of bones and joints
Genito-urinal tuberculosis
Cutaneous (skin) and subcutaneous
euberculosis
Tuberculosis of peripheral lymphatic nodes
Eye tuberculosis
Tuberculosis of other organs

B. Description of tubercular process specified according to process localization, clinical X-ray signs and presence or absence in diagnostic material of the patients Mycobacterium tuberculosis (MBT).

Localization and extent specified: in lungs according to lobes and segments; in other organs, according to localization of the damage.

Phase:

a) infiltration, disintegration, dissemination;
b) resolution, c
ondensation, scarring, calcification.

Bacterial expectoration:

a) with mycobacterium tuberculosis expectoration (MBT+)
b) without mycobacterium tuberculosis expectoration (MBT-).

C. Complications of tuberculosis:

Hemoptysis and lung hemorrhage, spontaneous pneumothorax, lung-heart insufficiency, atelectasis, amyloidosis, fistula and other.

D. Residual changes after treated tuberculosis.

a) breath organs: fibrous, fibrotic-focus, bullous-distrophy, calcinates in lungs and lymphatic nodes, pleuro-pneumosclerosis, cirrhosis, condition after surgical, operations and other.

b) other organs: scarring changes in different organs and their consequences, calcification, condition after surgical operations.

3.2. Primary and postprimary tuberculosis. ICD-10 classification.

Primary infection

Primary infection occurs in people who have not had any previous exposure to tubercle bacilli. Droplet nuclei, which are inhaled into the lungs, are so small that they avoid the mucociliary defences of the bronchi and lodge in the terminal alveoli of the lungs. Infection begins with multiplication of tubercle bacilli in the lungs. The resulting lesion is the Ghon focus. Lymphatics drain the bacilli to the hilar lymph nodes. The Ghon focus and related hilar lymphadenopathy form the primary complex. Bacilli may spread in the blood from the primary complex throughout the body. The immune response (delayed hypersensitivity and cellular immunity) develops about 4–6 weeks after the primary infection. The size of the infecting dose of bacilli and the strength of the immune response determine what happens next. In most cases, the immune response stops the multiplication of bacilli. However, a few dormant bacilli may persist. A positive tuberculin skin test would be the only evidence of infection. In a few cases the immune response is not strong enough to prevent multiplication of bacilli, and disease occurs within a few months.

Post-primary TB

Post-primary TB occurs after a latent period of months or years following primary infection. It may occur either by reactivation of the dormant tubercle bacilli acquired from a primary infection or by reinfection. Reactivation means that dormant bacilli persisting in tissues for months or years after primary infection start to multiply. This may be in response to a trigger, such as weakening of the immune system by HIV infection. Reinfection means a repeat infection in a person who has previously had a primary infection.

The immune response of the patient results in a pathological lesion that is characteristically localized, often with extensive tissue destruction and cavitation. Post-primary TB usually affects the lungs but can involve any part of the body. The characteristic features of post-primary TB are the following: extensive lung destruction with cavitation; positive sputu smear; upper lobe involvement; usually no intrathoracic lymphadenopathy. Patients with these lesions are the main transmitters of infection in the commmunity.

3.3. Tuberculosis in children. Progressive primary TB. Common and extra pulmonary symptoms(erythema nodosum, pharyngitis, joint inflammation phlyctenular conjunctivitis). Primary infectious complex (tuberculous mediastinal lymphadenitis and endobronchial tuberculosis). Progressive primary pulmonary tuberculosis. Reactivated pulmonary disease

The incidence and prevalence of pediatric tuberculosis (TB) worldwide varies significantly according to the burden of the disease in different countries. It has been estimated that 3.1 million children under 15 years of age are infected with TB worldwide. According to the World Health Organization (WHO), children with TB represent 10 to 20 % of all TB cases. The majority of these cases occur in lowincome countries where the prevalence of Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome (HIV/AIDS) is high. TB occurs frequently among disadvantaged populations, such as malnourished individuals, and those living in crowded areas. According to WHO reports, India, China, Pakistan, the Philippines, Thailand, Indonesia, Bangladesh, and the Democratic Republic of the Congo account for nearly 75 % of all cases of pediatric TB. Furthermore, it has also been reported that TB is responsible in Sub-Saharan countries for between 7 and 16 % of all episodes of acute pneumonia in HIV-infected children, and for approximately one fifth of all deaths in children presenting with acute pneumonia.

Tuberculosis in children is difficult to diagnose, even in its pulmonary form; children rarely produce sputum, so sputum smear examination can therefore not be used to obtain bacteriological proof, which is the cornerstone of diagnosis in adults. It is therefore diagnosed using a systematic approach whereby a number of clinical signs are interpreted.

TB disease in children is usually primary TB. Post-primary TB may occur in adults following reactivation of dormant TB bacilli acquired in childhood. The age when a child is infected determines the pattern of primary disease. Pulmonary disease in young children is closely linked to pathology of the mediastinal nodes. This is lymphobronchial TB, which results in a wide spectrum of segmental lesions. These lesions may also be found in adults, but are unusual. Young children (i.e. less than 5 years of age) are particularly susceptible to severe forms of disseminated disease following primary infection. These severe forms include miliary TB and extrapulmonary forms of TB, e.g. meningitis.

Tuberculosis disease presents in various clinical forms:

- primary pulmonary tuberculosis;
- acute disseminated tuberculosis: meningitis and miliary tuberculosis;
- post-primary pulmonary tuberculosis;
- extrapulmonary tuberculosis.

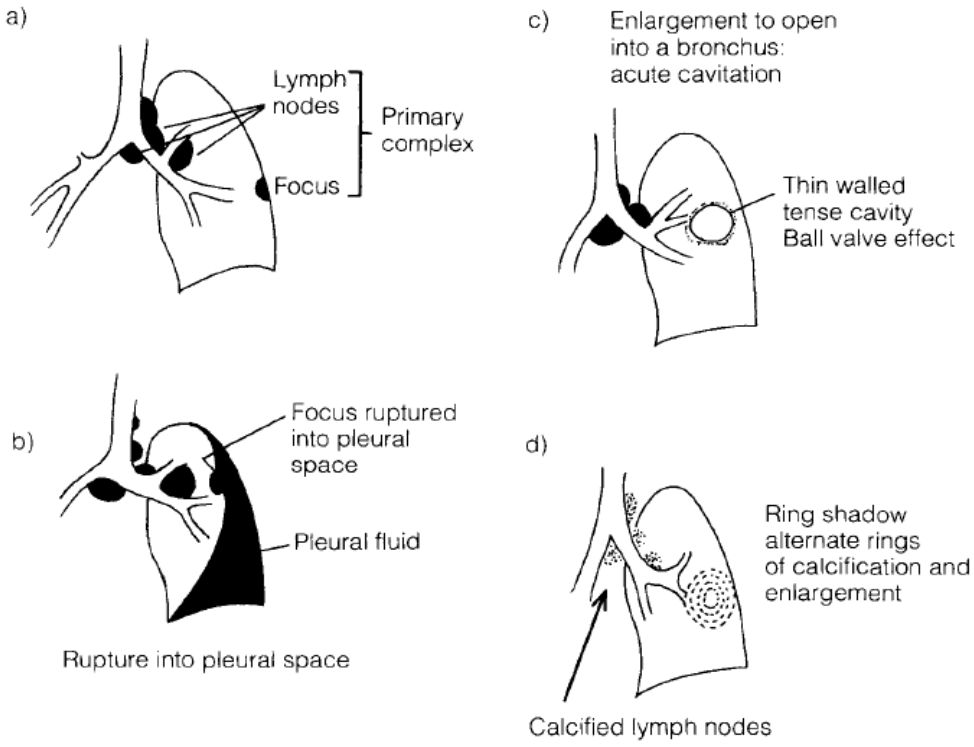


Figure 3.1 — Complications of primary tuberculosis complex

Primary pulmonary tuberculosis

The diagnosis of TB is particularly difficult in children because, under the age of 6–8 years, children with TB rarely cough up sputum. The readily available usual test for adults and older children with PTB is sputum smear microscopy. However, there is no such "gold standard" test for the majority of children with TB. Young children usually swallow their sputum. Gastric suction and laryngeal swabs are generally not useful unless facilities are available for *M. tuberculosis* culture. This means that bacteriological confirmation is usually not possible. The diagnosis of TB in children is therefore nearly always presumptive.

There are no specific features on clinical examination that can confirm that the presenting illness is due to TB. Respiratory symptoms and disease are extremely common in childhood, particularly before 5 years of age. In most cases of suspected TB, the child has been treated with a broad-spectrum antibiotic, with no clinical response. Always look for three important clues to TB in children:

1) Contact with an adult or older child with smear-positive PTB. It is usually possible to identify the source of infection. This is most often the child's mother or another female carer, such as an aunt, grandmother or older sister. They are the ones who spend most time with young children. Adult cases of PTB are occasionally diagnosed when a child presents with suspected TB.

2) Failure to thrive or weight loss (growth faltering). This is a good indicator of chronic disease in children and TB may be the cause. It is not specific and may also be due to poor nutrition, persistent or recurrent diarrhoea or HIV infection.

3) Respiratory symptoms such as cough lasting for more than three weeks in a child who has received a course of broad-spectrum antibiotics.

Primary infection is asymptomatic in the majority of cases, and goes unnoticed. This is termed infection and must be distinguished from disease. In 10 % of cases primary infection has clinical manifestations and presents with certain symptoms and radiographic abnormalities. Generalized symptoms are often subtle: slight fever, loss of weight, apathy and listlessness can attract the attention of the parents. Sometimes the symptoms are more obvious (e. g. a high fever of 39–40 °C and profound lethargy), and alert the parents to the fact that something is wrong. Mucocutaneous manifestations, although infrequent, are highly characteristic:

Erythema nodosum appears in the form of painful nodules on the shins, sometimes on the backs of the arms and rarely on the front, in two to three bursts. They are painful, red, raised lesions that may turn purple and take on the appearance of a bruise;

Phlyctenular conjunctivitis begins with generalized pain and irritation in one eye accompanied by watering and photophobia. On examination, grey or yellow lesions can be observed where the cornea joins the white of the eye; a number of blood vessels enter the lesions, giving an appearance of vascular engorgement of the conjunctiva. Each lesion persists for about a week, then disappears, to be replaced by others. In severe cases the cornea may ulcerate.

Radiological signs of primary pulmonary tuberculosis are characteristic. On postero-anterior and lateral radiography, the following may be observed:

- typical primary complex, the most frequent manifestation, consists of a small area of infiltration at any location in the lung parenchyma, accompanied by unilateral mediastinal lymphadenopathy. The infiltration forms when the bacilli are first inhaled (as a defence reaction around the location at which the bacilli first deposit); it is characteristically small (3 to 10mm in diameter). This nodular shadow is sometimes surrounded by a lighter, less dense shadow with irregular edges. On lateral X-ray, mediastinal lymphadenopathy appears as a rounded or oval latero-tracheal or hilar shadow.
- in some cases, isolated mediastinal lymphadenopathy may occur without any visible changes in the pulmonary parenchyma;
- occasionally, primary infection lesions may present as segmental (or lobar) consolidation associated with mediastinal lymphadenopathy. This is shadowing of a discrete area (usually right middle lobe, or lingula on the left), with clear margins and no bronchial markings, caused by compression of the (usually) middle lobe bronchus. It can mask the infiltration and even part of the causal lymphadenopathy.

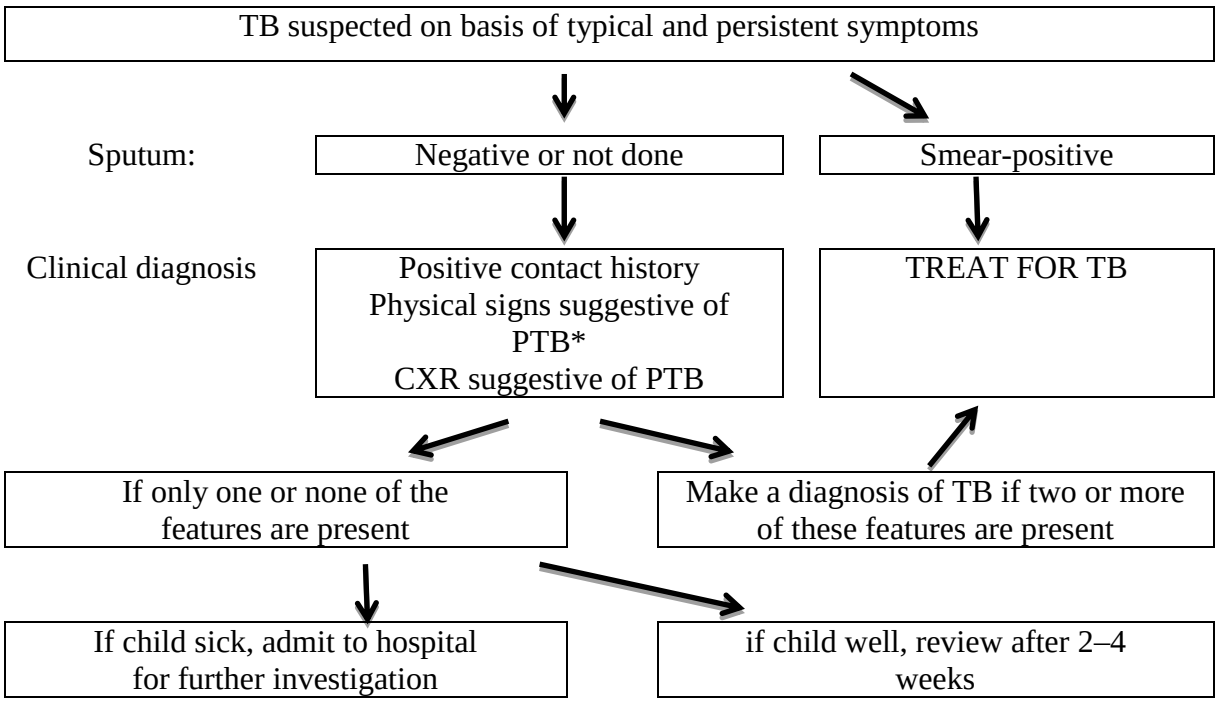


Figure 3.2 — Approach to diagnosis of TB in children

The courseof primary tuberculosis is usually benign, whether or not the child is treated, and most children recover completely without sequelae. They may, however, subsequently develop active tuberculosis (reactivate) after a period of quiescence.

Local complications of primary tuberculosis, while unusual, are well recognized:

fistulationof the lymph node into the bronchi: the lymph node swells and erodes into the bronchus (usually between the 4th and 7th month of development). This can be a serious event for small infants, where the caseous material can create acute bronchial obstruction; in older children it usually causescough;

the formation of a primary tuberculous cavity at the site of infiltration is a more unusual complication.

In both cases the child is usually incapable of producing sputum, but if a sample of bronchial or gastric aspiration is obtained, acid-fast bacilli can be recovered from smear microscopy.

Delayed local complications can result from the sequelae. Without treatment, lymphadenopathy can compress a lobar or segmental bronchus, creating breathing difficulties. Bronchiectasis may develop in the poorly ventilated area of the lung, creating bronchial superinfections and repeated episodes of haemoptysis. The most characteristic feature of this type of sequelae is «hilar disease» or «right middle lobe syndrome»: atelectasis, hilar calcification and recurrent haemoptysis. Antero-posterior and lateral X-ray will show systematic, very dense retractile shadowing, with concave edges, with some clear images and hilar calcifications in the center.

Acute forms of tuberculosis

These are early complications of primary infection (within 2–10 months). Caused by the dissemination of bacilli from the primary infection through the bloodstream, they can occur at all ages, but do so most often in very young children (< 2 years of age), particularly if they have not been vaccinated with BCG. They are serious, and are often fatal if diagnosed late.

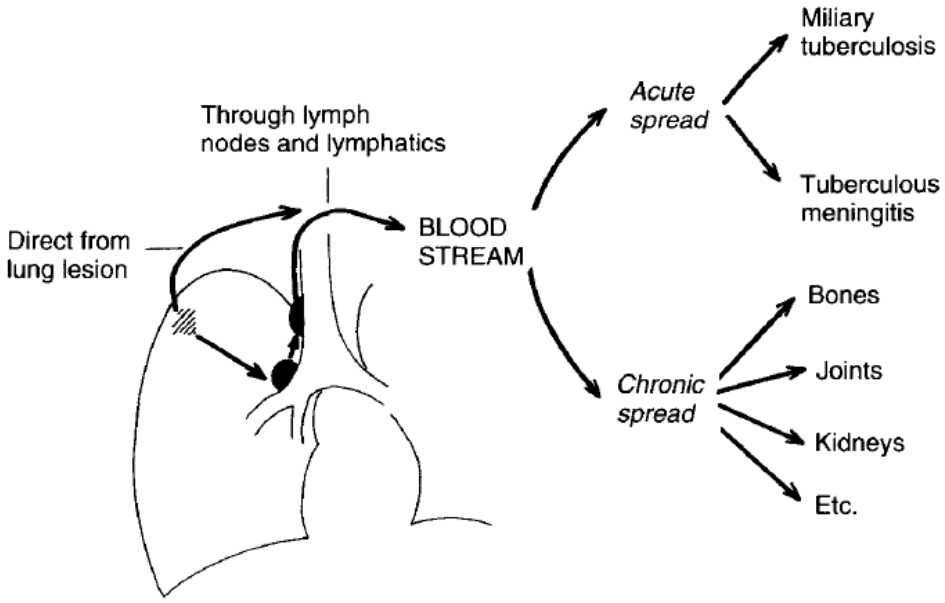


Figure 3.3 — The ways of generalization of tuberculous infection

3.4. Miliary disease

Disseminated or miliary TB

Disseminated tuberculosis is a form of the disease that affects many sites in the body simultaneously and is not limited to the lungs.

This is generalized, massive infection characterized by diffusion throughout the organism, of very small nodular elements («millet seeds»). It can occur immediately after primary infection or during reactivation of a latent site. Its onset may be either insidious or abrupt, depending on the bacillary load and/or the host immune situation, with unvaccinated infants, elderly and immunodeficient patients being the most susceptible.

Clinical manifestations are nonspecific and protean, depending on the predominant site of involvement. The clinical picture is completed in one to two weeks. Fever, night sweats, anorexia, weakness, and weight loss are presenting symptoms in the majority of cases. At times patients have a cough and other respiratory symptoms due to pulmonary involvement as well as abdominal symptoms. Physical findings include hepatomegaly, splenomegaly, and lymphadenopathy. Eye examination may reveal choroidal tubercles, which are pathognomonic of miliary tuberculosis, in up to 30 % of cases. Meningismus occurs in < 10 % of cases.

A high index of suspicion is required for the diagnosis of miliary tuberculosis. Frequently, chest radiography reveals a miliary reticulonodular pattern (more easily seen on underpenetrated film), although no radiographic abnormality may be evident early in the course and among HIV-infected patients. Other radiologic findings include large infiltrates, interstitial infiltrates (especially in HIV-infected patients), and pleural effusion.

Sputum smear microscopy is negative in 80 % of cases.

Various hematologic abnormalities may be seen, including anemia with leukopenia, lymphopenia, neutrophilic leukocytosis and leukemoid reactions, and polycythemia. Disseminated intravascular coagulation has been reported. Elevation of alkaline phosphatase levels and other abnormal values in liver function tests are detected in patients with severe hepatic involvement.

The TST may be negative in up to half of cases, but reactivity may be restored during chemotherapy.

Bronchoalveolar lavage and transbronchial biopsy are more likely to provide bacteriologic confirmation, and granulomas are evident in liver or bone-marrow biopsy specimens from many patients.

If it goes unrecognized, miliary tuberculosis is lethal; with proper early treatment, however, it is amenable to cure. Glucocorticoid therapy has not proved beneficial.

4. SECONDARY PULMONARY TUBERCULOSIS

4.1. Post-primary pulmonary TB. Clinical features depending on the inflammatory and immune response. Systemic and respiratory symptoms and signs of tuberculosis

In an adult, pulmonary tuberculosis may arise in a number of ways.

Progression of a primary lung infection in a person who has never previously been infected (previously tuberculin negative). In progressive primary tuberculosis in adults, the mid and lower parts of the lung are involved more frequently than the upper lung zones.

Progression of lung lesions comes from the blood spread of bacilli, which normally occurs after a primary lesion. These bacilli may end up in the lung as in other organs (Figure 3.1). If there are many bacilli and defences are poor, disseminated tuberculosis results. If there are only a few bacilli and defences are good, the bacilli may be killed. In between, lesions may start at one or both apices of the lung and later spread to other areas. This is an uncommon way for adult tuberculosis to develop.

Reactivation of an earlier primary infection, perhaps years after a childhood infection by TB (Figure 3.2 a-d). The patient's defences may have kept the lesion under control in childhood, but lowering of the patient's defences (e. g. by malnutrition, pregnancy, parturition or other diseases) may allow the TB to become active and spread the disease. In post-primary tuberculosis, the lesion is often in the apex or upper zone of the lung. The lung lesion is often more obvious than the lymph node enlargement, which you may not be able to detect on an X-ray. This is a common way for tuberculosis to develop in adults.

Reactivation of an old post-primary lesion that had been partially healed.

Re-infection may happen in persons previously infected with tuberculosis and progress to disease.

CLINICAL ASPECTS

Pulmonary TB in adults

The most frequent form of presentation of tuberculosis is disease that affects the lungs (pulmonary tuberculosis), while less frequent forms may affect any part of the body (extra-pulmonary tuberculosis) or present as acute disseminated tuberculosis.

Symptoms

The most important symptoms in the diagnosis of PTB are the following:

- cough for more than 2 or 3 weeks;
- sputum production;
- weight loss.

Over 90 % of patients with sputum smear-positive PTB develop a cough soon after disease onset. However, cough is not specific to PTB. Cough is common in smokers and in patients with acute upper or lower respiratory tract infection. Most acute respiratory infections resolve within 3 weeks. Therefore a patient with a cough for more than 2 or 3 weeks is a PTB suspect and must submit sputum samples for diagnostic microscopy.

Patients with PTB may also have other symptoms. These may be respiratory or constitutional (general or systemic).

Respiratory: chest pain, hemoptysis, breathlessness.

Constitutional: fever, night sweats, tiredness, loss of appetite, secondary amenorrhoea.

Physical signs

The physical signs in patients with PTB are nonspecific. They do not help to distinguish PTB from other chest diseases. There may be general signs, such as fever, tachycardia (fast pulse rate) and finger clubbing. Chest signs (heard through a stethoscope) may include crackles, wheezes, bronchial breathing and amphoric breathing. There are often no abnormal signs in the chest.

The first screening test for PTB suspects is sputum smear microscopy. In most cases of sputum smear-positive PTB a CXR is not necessary. In a few cases, a CXR may be necessary; the indications are as follows:

a) suspected complications in a breathless patient, needing specific treatment, e. g. pneumothorax, pericardial effusion or pleural effusion (note that a positive sputum smear is rare in pericardial effusion and pleural effusion);

b) frequent or severe haemoptysis (to exclude bronchiectasis or aspergilloma);

c) only 1 sputum smear positive out of 3 (in this case, an abnormal CXR is a necessary additional criterion for the diagnosis of sputum smear-positive PTB).

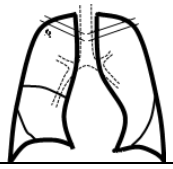
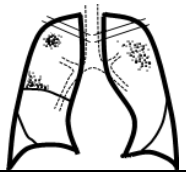
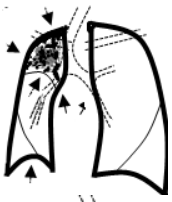
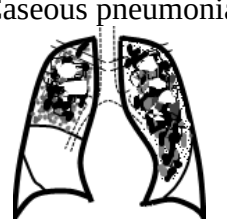
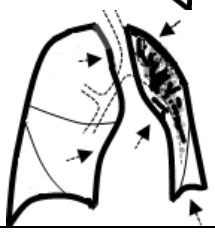
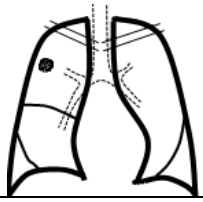
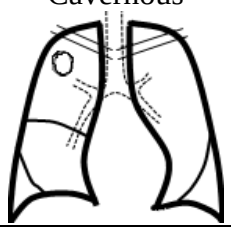
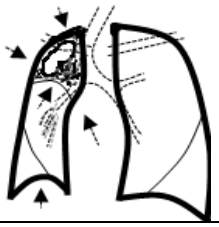
For practical purposes, a normal chest X-ray excludes tuberculosis. Very rarely, however, endobronchial tuberculosis or disease hidden by the mediastinum or diaphragm may look like a normal chest X-ray.

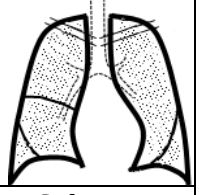
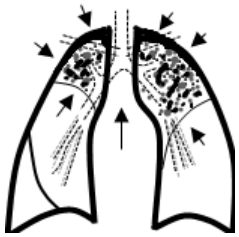
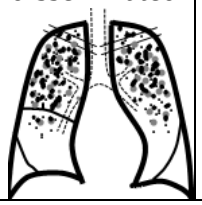
The following X-ray shadows are strongly suggest of tuberculosis:

upper lobe infiltrates or bilateral infiltrates
upper zone patchy or nodular shadows (on one or both sides)
cavitation
pulmonary fibrosis and shrinkage
oval or round solitary shadow
diffuse small nodular shadows (miliary tuberculosis)

If you suspect tuberculosis from the X-ray but the sputum is negative, give a non-tuberculosis antibiotic for 7–10 days then obtain another X-ray. Shadows of an acute pneumonia will show improvement.

Table 4.1 — Radiographic signs of pulmonary tuberculosis

X-ray appearence	Non-chronic forms (subacute and acute)	Chronic forms*
Focal shadow	Focal 	—
Patchy shadow	Infiltrative 	Cirrhotic 
Lobar shadow	Caseous pneumonia 	
Round shadow	Tuberculoma 	—
Ring formed shadow	Cavernous 	Fibrotic- cavernous 

<table>
<tr><td rowspan="2">Dissemination</td><td>Total monomorphic dissemination of low density, 2–3 mm, without confluence and cavitation</td><td>Miliary
  </td><td rowspan="2">Chronic disseminated
  </td></tr>
<tr><td>Upper and middle areas, polymorphic dissemination of low/ medium and high density, 5–10 mm, with confluence and cavitation</td><td>Subacute disseminated
  </td></tr>
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*volume decreasing affected area, shifting trachea, hilum, mediastinum and diaphragm to the affected side, linear shadow structure due to fibrosis

4.2. Acute progressive pulmonary TB. Risk factorsof acute TB progression,course and prognosis

Acute progressing TB disease is severe pulmonary affection which can be various by pathogenesis. It develops in predisposed patients with immunodeficiency and other risk factors. Clinical signs of phthisis are rapid onset, severe intoxication, hectic consumption, leanness and cachexia, extensive lung lesion and often TB generalization which predicts lethality. Fatal prognosis in spite of intensive treatment is typical for acute progressing TB disease.

Risk factors of acute TB progressing:

1. drug resistance of MBT;
2. HIV infection;
3. severe side effects of anti-TB drugs which make impossible adequate treatment application;
4. concomitant diseases such as diabetes, immunosuppression of various genesis, alcoholic debilitation, poor nutrition, etc.

Earlier described miliary tuberculosis is anacute TB form which is highly specific for primary progressing and HIV associated .tuberculosis. That is characterized by a wide hematogenous dissemination throughout the entire body (rare in an individual organ) and by the tiny size of the lesions (1–5 mm). The second one is caseous pneumonia which develops in predominated patients but without favorable conditions for hematogenous generalization.

Caseous pneumonia is an acute progressing TB form in which tubercles are not prominent, but with a diffuse extensive cellular infiltration that undergoes caseation that affects large areas of lung.

The symptoms of caseous pneumonia are determined by extension and intensity of inflammation. The disease starts acutely with hectic fever (40–41 °C in the evening and normal or even lower in the morning), sometime fever may become permanently high or low in terminal stage. Acute adinamia, weight loss,

profuse sweating, dyspnoea, chest pain, coughing with voluminous sputum are specific in such patients. Hemoptysis often occurs from erosed vessels. Profuse lung hemorrhage leading to asphyxia can become a reason offulminant death. X-ray visualizes massive, of the whole lobe or more, infiltration with giant cavities. Lesion spreads fast and often involves the whole lung. Bilateral total affection is not rear. Sputum is smear positive and the patients are highly contagious. Blood analysis shows ESR increasing and leucocytosis with toxic granulation. Lymphocytopenia frequently occurs which predicts unfavorable prognosis. In majority of cases patients' predisposition and acute progressing risk factors determine impossibility of curing and lethality rate in patients with caseous pneumonia is predictably high. If case is effectively cured cavities acquire fibrotic walls and caseous pneumonia transforms to chronic caverns. In little portion of casesifadvancedfibrosis and cirrhotic transformation predominate TB inflammation can gradually lose the activeness which may be followed by getting completely recovered.

4.3. Tuberculoma — pathogenesis, hystopathology and clinical aspects. Radiographic features and verification methods. Course and prognosis. Indication for surgical treatment

The lung tuberculoma — a special form of secondary tuberculosis, characterized by the development of lung dense caseous focus rounded form, separated from the surrounding tissue by a fibrous capsule.

The source of tuberculoma formation basically two forms of lung tuberculosis are served: infiltrative and focus. Besides tuberculoma could be formed from cavernous lung tuberculosis by means of filling of cavity with caseous masses.

Types of tuberculoma:

1) infiltrative-pneumonic tuberculoma − encapsulated quite fresh focus of caseous pneumonia;

2) caseoma is like the next step in the evolution of delimited ccaseous focus (desintegration, compaction, calcification, resorption);

3) filled cavity - pseudo-tuberculoma.

Variants of the tuberculoma aggravation;

1) development of the perifocal inflammation;

2) cavitation – discharge of the caseous masses from a cavity, through draining bronchus.

The term lung tuberculoma unites aetiologically various capsulated caseous focuses more than 1 cm in diameter cavities.

Tuberculoma can be single or multiple. Distinguished small tuberculoma (up to 2 cm in diameter), average (2–4 cm) and large (more than 4 cm in a diameter).

Three clinical variants of tuberculoma course are allocated:

1) progressing, described by occurrence at any stage of illness of disintegration, perifocal inflammation around tuberculoma, bronchogenic dissemination in surrounded lung tissue;

2) stable — absence of tuberculoma rentgenological changes or rare aggravations without signs of tuberculoma progressing;

3) regressing tuberculoma is characterized, by slow reduction in its size with the subsequent focus or group of focuses formation on its place, and of the field of indurations or combination of these changes.

The proportion tuberculoma among all forms of lung tuberculosis make 6–10 %. It is explained that large infiltrative pneumonic processes under influence of treatment and the increase of a host resistance becoming limited, are condensed, losing the aggravated course. Process recovers not completely, the precisely outlined dense formations remain in the places of infiltrations.

Clinical signs. As tuberculoma in itself is a parameter of high body resistance, frequently patients with this form of lung tuberculosis easy reveal casually, at fluorography examinations, routine examinations, at presence of other diseases. Practically the patients do not show complaints. At tuberculoma usually symptoms of intoxication, peculiar to tuberculosis: weakness, weight loss, sweating, cough, raise of temperature are absent. There are periods of expectoration of a big amount of sputum with inclusion of caseous grains.

At physical examination of the patient any pathological signs in lungs often usually are not presented. The crackles are listened only at massive inflammation with widespread infiltrative changes around tuberculoma or it's disintegration.

X-ray image of tuberculoma looks like rounded shadow with precise contours. Inside of the shadow circle form of enlightenment, boundary localized could be observed due to disintegration. Sometimes there are perifocal inflammation and small amount of bronchogenic focuses, and also calcification sites. Calcinated lymphatic nodes could be revealed In lungs roots. For tuberculema localization in II, I and VI segments are typical, more often in lateral position. The focuses could be revealed around tuberculoma, insignificant fibrosis, pleural deposits. Frequently tuberculoma is connected with visceral pleura by gentle bars.

The picture of blood without peculiarities, sometimes at acute stages moderate acceleration of ESR observed.

Mycobacterium tuberculosis is not found in sputum at stable course of tuberculoma, but at presence of disintegration bacilli expectoration meets if there is connection with drainage bronchus.

At the background of chemotherapy the tuberculoma is regressing or proceeding chronically without any aggravations among the 80 % of patients.

If in tuberculoma the disintegration is long kept and the patient continues to expectorate MBT, and prolong therapy does not give desirable results, the surgery intervention is recommended.

Surgical treatment. Usually operation is made with the minimal removal of lung tissue — segmenal resection. The surgical treatment is shown also in cases, when there is no certainty that the patient ill with tuberculosis and it is difficult to distinguish tubercular tuberculoma from other lung diseases.

5. CHRONIC TB DISEASE. DRUG RESISTANT TUBERCULOSIS. TUBERCULOSIS COMPLICATIONS

5.1. Reasons and conditions for developing of chronic pulmonary TB. Symptoms and course features of chronic TB disease. X-ray manifestation

The tuberculous granuloma gradually develops into a fibrous tubercle. Collagenous fibres invade the tuberculous focus, which is enclosed in a fibrous shell with fibroblasts and lymphocytes, forming a fibro-caseating granuloma that is then transformed into a fully fibrous tubercle. This focus can become entirely calcified. Chronic forms of TB disease develop as it lasts at least for 2 years which is enough for wide expressed lung fibrosis developing. The reasons for chronic forms occurring are following:

1. Late case-finding when the lung tissue is destructed and cavities have a rigid fibrotic wall due to which it cannot get cured.
2. Primary drug resistance of MBT which can be the reason of treatment fail.
3. Secondary drug resistance developing as a result of incorrect treatment application (especially if it is uncontrolled by medical stuff).
4. Patient's non-adherence to the treatment.

Chronic forms develop as a result of undulate progression of TB inflammation. Cavernous tuberculosis is intermediate form between infiltrative tuberculosis with lung tissue disintegration and chronic forms of pulmonary tuberculosis. This form is characterized by the presence of a thin-walled cavity without perifocal infiltration. The lung cavities have an external fibrotic capsule and contain undischarged caseous masses. X-ray examination shows a round cavity with a thin wall and which usually localizates in subclavicular area. The scarring and fibrous tissue is forming at long existence of a cavity so it becomes to be rigid. MBT and elastic fibres are found in sputum but the portion of patients may become smear-negative or for detection of MBT not only bacterioscopy, but culture method is necessary.

As a cavity exists longer than 2 years the sclerosis of surrounding tissue highly progresses which is specific for chronic pulmonary TB disease. Irregular change of progression and remission is representative for fibrous-cavernous pulmonary tuberculosis. Fibrotic cavity has a thick three-layered wall – the inner layer consists of caseous masses, the middle layer is performed by tubercular granulation tissue and the external layer of a cavity wall consists of the rigid fibrosis. The process can be unilateral and bilateral with one or many cavities. Focuses of bronchogenic dissemination are usual for chronic forms. High concentration of MBT which is often resistant to anti-TB drugs is specific. These patients represent the most epidemiologically dangerous contingent being the sources of TB infection in population.

If lung cirrhosis predominates (cirrhotic tuberculosis) then the concentration of MBT is not high and it may often not be found in sputum by

bacterioscopy but only by culture method. Such cases can be stabile and possible to get cured by long treatment courses.

For chronic TB forms the high frequency of pulmonary and non-pulmonary complications is specific, such as respiratory failure, haemophthysis, spontaneous pneumothorax, systemic amiloidosis and so on. Healing in such patients is often impossible especially in MDR-TB cases, and cachexia accompanied by different complications becomes the reason of lethal outcome.

5.2. Drug resistant tuberculosis. Reasons and mechanisms of drug resistance developing. Course and prognosis of drug resistant TB

Drug resistance in tuberculosis is the result of selection of resistant mutants in the bacterial population, due to killing of susceptible bacilli by anti-TB drugs. The problem is greatly exacerbated by inadequate treatment such as direct or indirect monotherapy, resulting from intake of a single anti-TB drug or from intake of several drugs with suboptimal concentrations. Susceptible bacilli are killed rapidly and resistant mutants are then able to multiply. Mycobacterium tuberculosis has the ability to undergo spontaneous, slow but constant mutation, resulting in resistant mutant organisms. This natural phenomenon is genetically determined and varies from drug to drug.

As with other infectious diseases, from staphylococcal infections to malaria, pathogens have almost invariably developed resistance to the drugs used to treat them. Tuberculosis is no exception: strains resistant to streptomycin were identified within months of the start of use, in the mid 1940 s, of this first antituberculosis drug. Indeed, the emergence of drug resistance was the primary reason that therapy for TB evolved to include treatment with more than one drug for up to 18 to 24 months — the standard of care for over two decades. The advent of rifampicin in the early 1970 s permitted a drastic reduction in the duration of therapy to six months while the efficacy of treatment improved. But in the mid-1990s, most countries participating in a global survey of anti-TB drug resistance registered cases of MDR-TB.

The main reason for the development of drug resistance is inadequate therapy.

Table 5.1 — Causes of inadequate antituberculosis treatment

Health-care providers: inadequate regimens	Drugs: inadequate supply or quality	Patients: inadequate drug intake
Inappropriate guidelines Noncompliance with guidelines Absence of guidelines Poor training No monitoring of treatment Poorly organized or funded TB control programs	Poor quality Unavailability of certain drugs (stock-outs or delivery disruptions) Poor storage conditions Wrong dose or combination	Poor adherence (or poor DOT) Lack of information Lack of money (no treatment available free of charge) Lack of transportation Adverse effects Social barriers Malabsorption Substance dependency disorders

Types of drug resistance.

Primary resistance is due to infection with a resistant strain, originating from a patient who has acquired resistance as a result of inadequate treatment. Thus the patient with primary resistance to a drug has never taken this drug in the past, but the original source of infection must have done so.

Acquired (secondary) resistance occurs when a patient is exposed to a single drug through failure of the program to ensure adherence to treatment, or because of selective drug intake, irregular drug supply, poor drug quality, inappropriate prescription, or, rarely, erratic absorption of medications. The growth of bacilli susceptible to that drug is suppressed, but multiplication of resistant organisms continues.

A «natural» drug-resistant strain is a wild strain that is resistant to a particular drug without ever having been in contact with it: neither the patient with naturally resistant bacilli nor the source of infection has received treatment with that drug in the past. This type of drug resistance is of little practical importance.

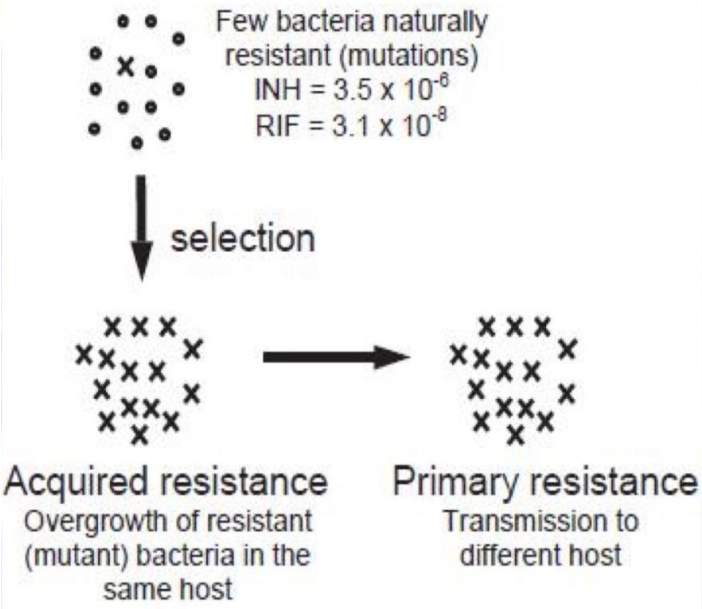

Figure 5.1 — Primary and acquired (secondary) resistance

Multidrug-resistant tuberculosis (MDR-TB), defined as TB caused by organisms that are resistant to isoniazid and rifampicin, two first-line anti-TB drugs. It can occur primarily (a patient infected by someone with MDR-TB) or secondarily (poor prior therapy). In most cases, resistance followed erratic treatments. MBT+ TB patients with resistant bacilli are as contagious as those infected by sensitive bacilli.

Mono or poly-drug resistance (PDR) – resistance to at least isoniazid or rifampicin but not both simultaneously or another first-line drugs. These patterns of resistance require adapted regimen in order to prevent possible evolution to MDR-TB under standard regimen

Extensive drug-resistant TB (XDR-TB), defined as MDR-TB that is resistant as well to any one of the fluoroquinolones and to at least one of three injectable second-line drugs (amikacin, capreomycin or kanamycin), has heightened this threat. XDR-TB has been identified in all regions of the world since 2006. Treatment outcomes are significantly worse in XDR-TB patients than in MDR-TB patients. Outbreaks of XDR-TB in populations with high prevalence of HIV have caused alarmingly high mortality rates.

A patient needs to be regularly monitored by a doctor during treatment of tuberculosis to determine if a strain of bacteria is susceptible or resistant to antibiotics. An individual may be displaying signs of drug resistance if:

• Symptoms do not improve during the first two months of treatment or worsen after initial improvement

• Sputum tests are not clear of bacteria after two months

• Sputum tests that have tested clear of bacteria again show evidence of bacteria

When drug resistance occurs, adjustments in treatment are necessary for the patient to recover. Physicians — preferably specialists who understand how to manage the disease — must go to greater lengths to bring about a cure, and despite their best efforts, they are sometimes unsuccessful.

Less than 50 percent of patients with resistant strains of tuberculosis recover with treatment, compared to over 90 percent of patients with nonresistant strains. Because of the contagiousness and tenacity of resistant infections, initial treatment should always take place in a hospital setting. There the patient can be monitored for progress and for side effects of the large doses of drugs needed to fight the disease. Therapy is as grueling as cancer chemotherapy, and can be an extremely lonely experience because patients must remain isolated. It includes taking at least six antibiotics concurrently, and at least two of these must kill rather than simply inhibit bacterial growth. Difficulty sometimes arises in finding antibiotics to which resistant bacteria respond. In order to weaken bacteria and allow the body to fight the disease, doctors must continually adjust dosages and sometimes turn to medicines that are not as effective or that have highly undesirable side effects such as personality changes and psychosis.

The sickest patients sometimes take as many as sixteen pills daily and a series of shots several times a week to suppress infection. Treatment often lasts for two years rather than the six to eighteen months needed for standard treatment.

5.3. Respiratory complications of TB. Hemoptysis and lung hemorrhage — diagnostic approach and management. Spontaneous pneumothorax. Closed and tension pneumothorax. Signs and symptoms, diagnostic and management. Urgent needle decompression of the pleural cavity. TB fistula. empyema and atelectasis

Hemoptysis is coughing up of blood from the respiratory tract. Massive hemoptysis is production of ≥ 600 mL of blood within 24 h.

Most of the lung's blood (95%) circulates through low-pressure pulmonary arteries and ends up in the pulmonary capillary bed, where gas is exchanged. About 5 % of the blood supply circulates through high-pressure bronchial arteries, which originate at the aorta and supply major airways and supporting structures. In haemoptysis, the blood generally arises from this bronchial circulation, except when pulmonary arteries are damaged by trauma, by erosion of a granulomatous or calcified lymph node or tumor, or, rarely, by pulmonary arterial catheterization or when pulmonary capillaries are affected by inflammation.

Physical examination: Vital signs are reviewed for fever, tachycardia, tachypnea, and low O_2 saturation. Constitutional signs (e. g., cachexia) and level of patient distress (e. g., accessory muscle use, pursed lip breathing, agitation, dicreased level of consciousness) should also be noted.

A full lung examination is done, particularly including adequacy of air entry and exit, symmetry of breath sounds, and presence of crackles, rhonchi, stridor, and wheezing. Signs of consolidation (e. g., egophony, dullness to percussion) should be sought. The cervical and supraclavicular areas should be inspected and palpated for lymphadenopathy (suggesting cancer or TB).

Neck veins should be inspected for distention, and the legs and presacral area should be palpated for pitting edema (suggesting heart failure). Heart sounds should be auscultated with notation of any extra heart sounds or murmur that might support a diagnosis of heart failure and elevated pulmonary pressure.

The abdominal examination should focus on signs of hepatic congestion or masses, which could suggest either cancer or hematemesis from potential esophageal varices.

The skin and mucous membranes should be examined for ecchymosis, petechiae, telangiectasia, gingivitis, or evidence of bleeding from the oral or nasal mucosa.

If the patient can reproduce hemoptysis during examination, the color and amount of blood should be noted.

The following findings are of particular concern:

- Massive hemoptysis.
- Back pain.
- Presence of a pulmonary artery catheter or tracheostomy.
- Malaise, weight loss, or fatigue.
- Extensive smoking history.
- Dyspnea at rest during examination or absent or decreased breath sounds.

Treatment

Massive hemoptysis. Initial treatment of massive hemoptysis has two objectives:

- Prevent aspiration of blood into the uninvolved lung (which can cause asphyxiation).
- Prevent exsanguination from ongoing bleeding.

It can be difficult to protect the uninvolved lung because it is often initially unclear which side is bleeding. Once the bleeding side is identified, strategies include positioning the patient with the bleeding lung in a dependent position and selectively intubating the uninvolved lung and/or obstructing the bronchus going to the bleeding lung.

Prevention of exsanguination involves reversal of any bleeding diathesis and direct efforts to stop the bleeding. Clotting deficiencies can be reversed with fresh frozen plasma and factor-specific or platelet transfusions. Laser therapy, cauterization, or direct injection with epinephrine or vasopressin can be done bronchoscopically.

Massive hemoptysis is one of the few indications for rigid (as opposed to flexible) bronchoscopy, which provides control of the airway, allows for a larger field of view than flexible bronchoscopy, allows better suctioning, and is more suited to therapeutic interventions, such as laser therapy.

Embolization via bronchial artery angiography is becoming the preferred method with which to stop massive hemoptysis, with reported success rates of up to 90 %. Emergency surgery is indicated for massive hemoptysis not controlled by rigid bronchoscopy or embolization and is generally considered a last resort.

Spontaneous pneumothorax.

Air is not normally present between the visceral and parietal pleural surfaces. However, air can be introduced into the pleural space by a break in the surface of either pleural membrane, thus creating a pneumothorax.

A pneumothorax can result from a break in the parietal pleura (e. g., from trauma, needle or catheter insertion) or in the visceral pleura (e. g., from rupture of a subpleural air pocket, necrosis of lung adjacent to the pleura).

Intrapleural pressure is normally negative (less than atmospheric pressure) because of inward lung and outward chest wall recoil. In pneumothorax, air enters the pleural space from outside the chest or from the lung itself via mediastinal tissue planes or direct pleural perforation. Intrapleural pressure increases, and lung volume decreases.

Tension pneumothorax is a pneumothorax causing a progressive rise in intrapleural pressure to levels that become positive throughout the respiratory cycle and collapses the lung, shifts the mediastinum, and impairs venous return to the heart. Air continues to get into the pleural space but cannot exit. Without appropriate treatment, the impaired venous return can cause systemic hypotension and respiratory and cardiac arrest (pulseless electrical activity) within minutes.

Symptoms and Signs

Small pneumothorax is occasionally asymptomatic. Symptoms of pneumothorax include dyspnea and pleuritic chest pain. Dyspnea may be sudden or gradual in onset depending on the rate of development and size of the pneumothorax. Pain can simulate pericarditis, pneumonia, pleuritis, pulmonary embolism, musculoskeletal injury (when referred to the shoulder), or an intra-abdominal process (when referred to the abdomen). Pain can also simulate cardiac ischemia, although typically the pain of cardiac ischemia is not pleuritic.

Physical findings classically consist of absent tactile fremitus, hyperresonance to percussion, and decreased breath sounds on the affected side. If the pneumothorax is large, the affected side may be enlarged with the trachea visibly shifted to the opposite side. With tension pneumothorax, hypotension can occur.

Diagnosis

The diagnosis is suspected in stable patients with dyspnea or pleuritic chest pain and is confirmed with upright inspiratory chest x-ray. Radiolucent air and the absence of lung markings juxtaposed between a shrunken lobe or lung and the parietal pleura are diagnostic of pneumothorax. Tracheal deviation and mediastinal shift occur with large pneumothoraces.

Treatment

- Immediate needle decompression for tension pneumothorax.
- Observation and follow-up x-ray for small, asymptomatic, primary spontaneous pneumothorax.
- Catheter aspiration for large or symptomatic primary spontaneous pneumothorax.
- Tube thoracostomy for secondary and traumatic pneumothorax.

Patients should receive supplemental O_2 until chest x-ray results are available because O_2 accelerates pleural reabsorption of air. Treatment then depends on the type, size, and effects of the pneumothorax. Primary spontaneous pneumothorax that is < 20 % and that does not cause respiratory or cardiac symptoms can be safely observed without treatment if follow-up chest x-rays done at about 6 and 48 h show no progression. Larger or symptomatic primary spontaneous pneumothorax should be evacuated by catheter aspiration. Tube thoracostomy is an alternative.

Catheter aspiration is accomplished by insertion of a small-bore or pigtail catheter into the chest in the 2nd intercostal space at the midclavicular line. The catheter is attached to a 3-way stopcock and syringe. Air is withdrawn from the pleural space through the stopcock into the syringe and expelled into the room.

TB fistula. empyema and atelectasis

In chronic patients TB inflammation can directly spread from lung tissue and lymph nodes to bronchi. As a result bronchial fistula may occur. Tuberculous empyema is a less common complication of pulmonary tuberculosis. It is usually the result of the rupture of a cavity, with spillage of a large number of organisms into the pleural space. This process may create a bronchopleural fistula with evident air in the pleural space. A chest radiograph shows hydropneumothorax with an air-fluid level. The pleural fluid is purulent and thick and contains large numbers of lymphocytes. Acid-fast smears and mycobacterial cultures are often positive. Surgical drainage is usually required as an adjunct to chemotherapy. Tuberculous empyema may result in severe pleural fibrosis and restrictive lung disease. Removal of the thickened visceral pleura (decortication) is occasionally necessary to improve lung function.

Atelectasis can result from an blockage of the airways by stricture or compression with swelled nearby lymph nodes. Chest X ray shows an airless

area looking as a triangle shadow. If airways do not get restored in short time then atelectasis can persist over months and years. Airless lung tissue gets scared due to what fibroatelectasis become irreversible.

5.4. Systemic TB complications — Pulmonary hypertensionwithlung-heart insufficiency, secondary amyloidosis

Pulmonary hypertension often complicates chronic lung diseases. Pulmonary hypertension is an increase of blood pressure in the pulmonary artery, pulmonary vein and capillaries (lung vasculature). In hypoxic pulmonary hypertension the low levels of oxygen are thought to cause vasoconstriction or tightening of pulmonary arteries. This phenomenon is called hypoxic pulmonary vasoconstriction and it is initially a protective response designed to stop too much blood flowing to areas of the lung that are damaged and do not contain oxygen. When the damage is widespread and prolonged, this hypoxia-mediated vasoconstriction occurs across a large portion of the pulmonary vascular bed. This further increases the blood pressure within the lungs and impairs their blood flow. The increased workload of the heart causes hypertrophy of the right ventricle, making the heart less able to pump blood through the lungs, ultimately causing right heart failure (cor pulmonale). The right ventricle is normally part of a low pressure system, with pressures that are around one-sixth of those that the left ventricle has to deal with. As such, the right ventricle is much less able to cope as pressure rises, and although hypertrophy of the heart muscle helps initially, it ultimately leads to a situation where the right ventricular muscle cannot get enough oxygen to meet its needs and right heart failure follows. As the blood flowing through the lungs decreases, the left side of the heart receives less blood. This blood may also carry less oxygen than normal. Therefore it becomes harder and harder for the left side of the heart to pump to supply sufficient oxygen to the rest of the body, especially during physical activity.

The molecular mechanism of pulmonary hypertension is not known yet, but it is believed that the endothelial dysfunction results in a decrease in the synthesis of endothelium-derived vasodilators such as nitric oxide and prostacyclin. Moreover, there’s a stimulation of the synthesis of vasoconstrictors such as thromboxane and vascular endothelial growth factor. Patients with PH produce less NO and others vasodilators and produce more vasoconstrictors. Consequently, this molecular pathway doesn’t work properly and it results in a constant vasoconstriction.

Diagnostic approaches

Normal pulmonary arterial pressure has a mean value of 8–20 mm Hg at rest. Pulmonary hypertension is present when mean pulmonary artery pressure exceeds 25 mm Hg. Although pulmonary arterial pressure can be definitely estimated by pressure measurements with right-sided cardiac catheterization, it is not practical in patients with chronic TB forms. The presence of pulmonary hypertension can be confirmed by following investigations: pulmonary function tests, electrocardiography, Doppler echocardiography, chest X-ray.

A physical examination is performed to look for typical signs of pulmonary hypertension. These include altered heart sounds, such as a widely split S_2 or second heart sound, a loud P_2 or pulmonic valve closure sound (part of the second heart sound), (para)sternal heave, possible S_3 or third heart sound, and pulmonary regurgitation. Other signs include an elevated jugular venous pressure, peripheral edema, ascites, nail clubbing.

Pulmonary function tests show obstructive and restrictive disorders that starts the mechanism of pulmonary hypertension owing to lung diseases and/or hypoxia. *The electrocardiogram* may demonstrate signs of right ventricular hypertrophy or right atrial enlargement in pulmonary hypertension.

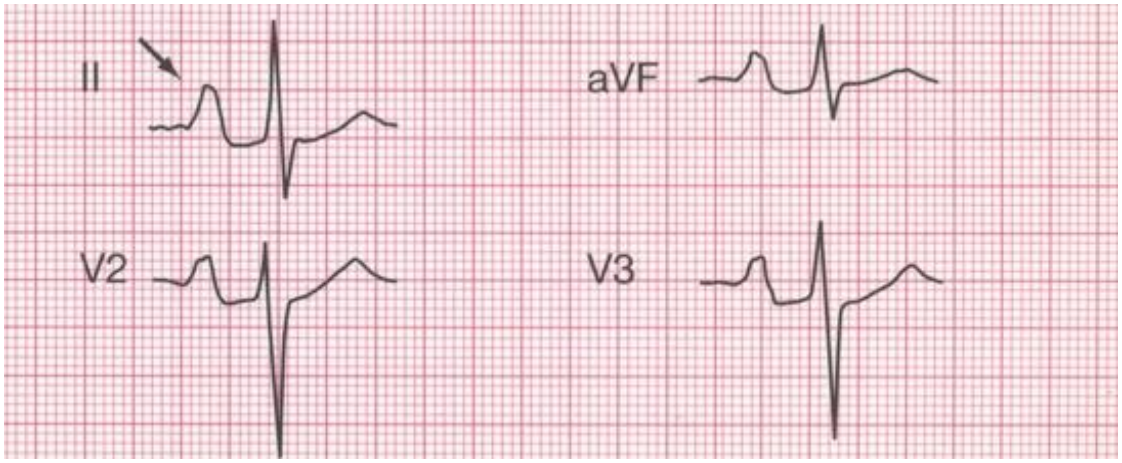

Figure 5.1 — ECG findings include right axis deviation, P-pulmonale, right bundle branch block, and R/S ratio >1 in lead V_1. The higher the pulmonary artery pressure, the more sensitive is the ECG. Arrhythmias often occur in patients with cor pulmonale

Echocardiography with Doppler studies is the most useful first line investigation in a patient presenting with clinical features suggestive of pulmonary hypertension. It facilitates estimation of pulmonary artery systolic pressure to determine if PH is present and assessment of severity of RV dysfunction. The estimation of PAP is based on the peak velocity of the jet of tricuspid regurgitation. Echocardiography also detects the backward flow between the right ventricle and right atrium which normally absent. *Chest radiography* is inferior to ECG in detecting pulmonary hypertension. Although insensitive, a right descending pulmonary artery diameter > 16 mm on standard chest x-ray is specific for pulmonary hypertension.

Therapy

Anti-TB therapy remains to be the cornerstone of treating pulmonary hypertension associated with tuberculosis It should be added by oxygen therapy and vasoactive agents such as prostanoids, phosphodiesterase inhibitors. endothelin antagonists calcium channel blockers. Digoxin is not indicated as it increases myocardium oxygen need which can not be satisfied. Diuretics should not be widely prescribed due to risk of aggravating hypercoagulation.

Secondary (reactive) amyloidosis is a less common complication of predominantly chronic TB forms. Amyloid is a complex protein, the exact chemical composition of which has not yet been definitely determined. Secondary amyloidosis develops due to disturbance of protein metabolism. When the normally soluble proteins fold to become amyloids, they become insoluble and deposit in organs or tissues, disrupting normal function. The amyloid tissue deposit in tuberculosis and other chronic infections is AA proteins (SAA — serum amyloid A protein) which is an acute-phase reactant that is produced in inflammation. Deposition can be systemic (affecting many different organ systems) or organ-specific. Amyloidosis frequently affects the heart, kidneys, liver, spleen, nervous system and digestive tract. Severe amyloidosis can lead to life-threatening organ failure. Diagnostic bases on the organ biopsy. The treatment of patients' secondary amyloidosis is directed at treating the underlying illness.

6. EXTRAPULMONARY TUBERCULOSIS

Tuberculosis that affects any organ outside the pulmonary parenchyma is designated extrapulmonary tuberculosis. In addition to all the sites of the body outside the chest affected by tuberculosis that are clearly extrapulmonary, certain forms of tuberculosis occurring in sites that are fully or partially within the chest are also considered extrapulmonary:

Pleural tuberculosis and tuberculosis of the hilar or mediastinal lymph nodes are classified as extrapulmonary, provided there are no discernible lung parenchymal abnormalities.

6.1. Tuberculous meningoencephalitis — risk factors and clinical features. Lumbar puncture and examination of the cerebrospinal fluid. Cerebral tuberculoma - clinical aspects, course and prognosis

Tuberculous Meningitis and Tuberculoma

Tuberculosis of the central nervous system (CNS) is seen most often in young children but also develops in adults, especially those infected with HIV. Tuberculous meningitis results from the hematogenous spread of primary or postprimary pulmonary disease or from the rupture of a subependymal tubercle into the subarachnoid space. In more than half of cases, evidence of old pulmonary lesions or a miliary pattern is found on chest radiography. The disease often presents subtly as headache and slight mental changes after a prodrome of weeks of low-grade fever, malaise, anorexia, and irritability. If not recognized, tuberculous meningitis may evolve acutely with severe headache, confusion, lethargy, altered sensorium, and neck rigidity. Typically, the disease evolves over 1–2 weeks, a course longer than that of bacterial meningitis. Paresis of cranial nerves (ocular nerves in particular) is a frequent finding, and the involvement of cerebral arteries may produce focal ischemia. The ultimate evolution is toward coma, with hydrocephalus and intracranial hypertension.

Lumbar puncture is the cornerstone of diagnosis. In general, examination of the cerebrospinal fluid (CSF) reveals a high leukocyte count (up to 1000/L), usually with a predominance of lymphocytes but sometimes with a predominance of neutrophils in the early stage; a protein content of 1–8 g/L (100–800 mg/dL); and a low glucose concentration. However, any of these three parameters can be within the normal range. AFB are seen on direct smear of CSF sediment in up to one-third of cases, but repeated lumbar punctures increase the yield. Culture of CSF is diagnostic in up to 80 % of cases and remains the gold standard. Polymerase chain reaction (PCR) has a sensitivity of up to 80 %, but rates of false-positivity reach 10 %. The ADA concentration may be a sensitive test but has low specificity. Imaging studies (CT and MRI) may show hydrocephalus and abnormal enhancement of basal cisterns or ependyma.

If unrecognized, tuberculous meningitis is uniformly fatal. This disease responds to chemotherapy; however, neurologic sequelae are documented in 25 % of treated cases, in most of which the diagnosis has been delayed. Clinical trials have demonstrated that patients given adjunctive glucocorticoids may experience faster resolution of CSF abnormalities and elevated CSF pressure. In a recent study, adjunctive dexamethasone (0,4 mg/kg per day given IV and tapering by 0,1 mg/kg per week until the fourth week, when 0,1 mg/kg per day was administered; followed by 4 mg/d given by mouth and tapering by 1 mg per week until the fourth week, when 1 mg/d was administered) significantly enhanced the chances of survival among persons > 14 years of age but did not reduce the frequency of neurologic sequelae.

Tuberculoma, an uncommon manifestation of CNS tuberculosis, presents as one or more space-occupying lesions and usually causes seizures and focal signs. CT or MRI reveals contrast-enhanced ring lesions, but biopsy is necessary to establish the diagnosis.

6.2. Pleural tuberculosis — pathogenesis and clinical aspects. Phisical signs and radiographic features. Thoracentesis examination of the pleural fluid. Tuberculosis of the upper airways. Indication for bronchoscopy

Pleural Tuberculosis

Involvement of the pleura is common in primary tuberculosis and may result from either contiguous spread of parenchymal inflammation or, as in many cases of pleurisy accompanying postprimary disease, actual penetration by tubercle bacilli into the pleural space. Depending on the extent of reactivity, the effusion may be small, remain unnoticed, and resolve spontaneously or may be sufficiently large to cause symptoms such as fever, pleuritic chest pain, and dyspnea. Physical findings are those of pleural effusion: dullness to percussion and absence of breath sounds. A chest radiograph reveals the effusion and, in up to one-third of cases, also shows a parenchymal lesion.

Thoracentesis is required to ascertain the nature of the effusion and to differentiate it from manifestations of other etiologies. The fluid is straw-colored

and at times hemorrhagic; it is an exudate with a protein concentration > 50 % of that in serum (usually ~ 4–6 g/dL), a normal to low glucose concentration, a pH of ~7,3 (occasionally <7,2), and detectable white blood cells (usually 500–6000/L). Neutrophils may predominate in the early stage, while mononuclear cells are the typical finding later. Mesothelial cells are generally rare or absent. AFB are seen on direct smear in only 10–25 % of cases, but cultures may be positive for M. tuberculosis in 25–75 % of cases; positive cultures are more common among postprimary cases. Determination of the pleural concentration of adenosine deaminase (ADA) is a useful screening test: tuberculosis is virtually excluded if the value is very low. Needle biopsy of the pleura is often required for diagnosis and reveals granulomas and/or yields a positive culture in up to 80 % of cases. This form of pleural tuberculosis responds well to chemotherapy and may resolve spontaneously. The usefulness of glucocorticoid administration is doubtful.

Tuberculosis of the Upper Airways

Nearly always a complication of advanced cavitary pulmonary tuberculosis, tuberculosis of the upper airways may involve the larynx, pharynx, and epiglottis. Symptoms include hoarseness, dysphonia, and dysphagia in addition to chronic productive cough. Findings depend on the site of involvement, and ulcerations may be seen on laryngoscopy. Acid-fast smear of the sputum is often positive, but biopsy may be necessary in some cases to establish the diagnosis. Carcinoma of the larynx may have similar features but is usually painless.

6.3. Peripheral lymph node TB. Genitourinary and genital TB. Skeletal tuberculosis. Less common extrapulmonary forms (gastrointestinal tuberculosis, tuberculous pericarditis and other)

Lymph-node tuberculosis (tuberculous lymphadenitis)

This form of tuberculosis, which occurs relatively early after primary infection with Mycobacterium tuberculosis, often affects young people in countries with a high prevalence of tuberculosis.

Lymph-node tuberculosis presents as painless swelling of the lymph nodes, most commonly at posterior cervical and supraclavicular sites (a condition historically referred to as scrofula). Lymph nodes are usually discrete and nontender in early disease but may be inflamed and have a fistulous tract draining caseous material. Associated pulmonary disease is seen in > 40 % of cases. Systemic symptoms are usually limited to HIV-infected patients. The diagnosis is established only by fine-needle aspiration or surgical biopsy. AFB are seen in up to 50 % of cases, cultures are positive in 70–80 %, and histologic examination shows granulomatous lesions.

Differential diagnosis includes a variety of infectious conditions, neoplastic diseases such as lymphomas or metastatic carcinomas.

Genitourinary Tuberculosis

Genitourinary tuberculosis may involve any portion of the genitourinary tract. Local symptoms predominate, and up to one-third of patients may

concomitantly have pulmonary disease. Urinary frequency, dysuria, nycturia, hematuria, and flank or abdominal pain are the common presentations. However, patients may be asymptomatic and the disease discovered only after severe destructive lesions of the kidneys have developed. Urinalysis gives abnormal results in 90 % of cases, revealing pyuria and hematuria. The documentation of culture-negative pyuria in acidic urine raises the suspicion of tuberculosis. Intravenous pyelography, abdominal CT, or MRI may show deformities and obstructions, and calcifications and ureteral strictures are suggestive findings. Culture of three morning urine specimens yields a definitive diagnosis in nearly 90 % of cases. Severe ureteral strictures may lead to hydronephrosis and renal damage.

Genital tuberculosis is diagnosed more commonly in female than in male patients. In female patients, it affects the fallopian tubes and the endometrium and may cause infertility, pelvic pain, and menstrual abnormalities. Diagnosis requires biopsy or culture of specimens obtained by dilatation and curettage. In male patients, tuberculosis preferentially affects the epididymis, producing a slightly tender mass that may drain externally through a fistulous tract; orchitis and prostatitis may also develop. In almost half of cases of genitourinary tuberculosis, urinary tract disease is also present. Genitourinary tuberculosis responds well to chemotherapy.

Skeletal Tuberculosis

In bone and joint disease, pathogenesis is related to reactivation of hematogenous foci or to spread from adjacent paravertebral lymph nodes. Weight-bearing joints (the spine in 40 % of cases, the hips in 13 %, and the knees in 10 %) are most commonly affected. Spinal tuberculosis (Pott's disease or tuberculous spondylitis) often involves two or more adjacent vertebral bodies. While the upper thoracic spine is the most common site of spinal tuberculosis in children, the lower thoracic and upper lumbar vertebrae are usually affected in adults. From the anterior superior or inferior angle of the vertebral body, the lesion slowly reaches the adjacent body, later affecting the intervertebral disk. With advanced disease, collapse of vertebral bodies results in kyphosis (gibbus). A paravertebral «cold» abscess may also form. In the upper spine, this abscess may track to and penetrate the chest wall, presenting as a soft tissue mass; in the lower spine, it may reach the inguinal ligaments or present as a psoas abscess. CT or MRI reveals the characteristic lesion and suggests its etiology.

The differential diagnosis includes tumors and other infections. Pyogenic bacterial osteomyelitis, in particular, involves the disk very early and produces rapid sclerosis. Aspiration of the abscess or bone biopsy confirms the tuberculous etiology, as cultures are usually positive and histologic findings highly typical. A catastrophic complication of Pott's disease is paraplegia, which is usually due to an abscess or a lesion compressing the spinal cord. Paraparesis due to a large abscess is a medical emergency and requires rapid drainage. Tuberculosis of the hip joints, usually involving the head of the femur, causes pain; tuberculosis of the knee produces pain and swelling. If the disease goes unrecognized, the joints may be destroyed. Diagnosis requires examination of the synovial fluid, which is thick in

appearance, with a high protein concentration and a variable cell count. Although synovial fluid culture is positive in a high percentage of cases, synovial biopsy and tissue culture may be necessary to establish the diagnosis. Skeletal tuberculosis responds to chemotherapy, but severe cases may require surgery.

Gastrointestinal Tuberculosis

Gastrointestinal tuberculosis is uncommon. Various pathogenetic mechanisms are involved: swallowing of sputum with direct seeding, hematogenous spread, or (largely in developing areas) ingestion of milk from cows affected by bovine tuberculosis. Although any portion of the gastrointestinal tract may be affected, the terminal ileum and the cecum are the sites most commonly involved. Abdominal pain (at times similar to that associated with appendicitis) and swelling, obstruction, hematochezia, and a palpable mass in the abdomen are common findings at presentation. Fever, weight loss, anorexia, and night sweats are also common. The yield of direct smear and culture is relatively low, biopsy (with a specimen best obtained by laparoscopy) is often needed to establish the diagnosis. In the majority of cases gastrointestinal tuberculosis is one of manifestation of TB generalization.

Less Common Extrapulmonary Forms

Tuberculosis may cause chorioretinitis, uveitis, panophthalmitis, and painful hypersensitivity-related phlyctenular conjunctivitis.

Cutaneous manifestations of tuberculosis include primary infection due to direct inoculation, abscesses and chronic ulcers, scrofuloderma, lupus vulgaris (a smoldering disease with nodules, plaques, and fissures), miliary lesions, and erythema nodosum.

Tuberculous pericarditis develops due to direct progression of a primary focus within the pericardium, to reactivation of a latent focus, or to rupture of an adjacent subcarinal lymph node, pericardial tuberculosis has often been a disease of the elderly in countries with low tuberculosis prevalence but also develops frequently in HIV-infected patients.

Tuberculous otitis is rare and presents as hearing loss, otorrhea, and tympanic membrane perforation.

Adrenal tuberculosis presents as adrenal insufficiency.

These forms also occur as a manifestation of disseminated disease.

7. TUBERCULOSIS ACCOMPANIED BY OTHER DISEASES AND SPECIAL SITUATIONS

7.1. Tuberculosis and HIV infection. Clinical aspects of HIV-TB. Course and prognosis for tuberculosis depending on stage of HIV-infection.

HIV-Associated Tuberculosis

HIV infection is the most powerful risk factor that increases the likelihood of development of tuberculosis in a person previously infected with Mycobacterium tuberculosis. HIV-associated tuberculosis is included in the current international AIDS definition.

The circumstances of diagnosis are variable: tuberculosis may occur in individuals infected with HIV, while at other times it may be diagnosed in individuals whose HIV status is unknown; it is thus frequently the sentinel event that indicates HIV infection.

Cough for more than a month and recurrent pneumonia may be associated with other complications of HIV infection. As recurrent pneumonia due to other pathogens frequently occurs in HIV-infected patients, it should be kept in mind that seropositive patients with respiratory symptoms and abnormalities on chest X-ray should not always be assumed to have tuberculosis, and that the diagnosis of pulmonary tuberculosis should be based on criteria as rigorous as those for seronegative patients. Nevertheless, if a HIV-positive patient has persistent cough, investigations should systematically be made to check for the presence of tuberculosis.

The diagnosis of tuberculosis in HIV-infected patients may be difficult not only because of the increased frequency of sputum-smear negativity (up to 40% in culture-proven pulmonary cases) but also because of atypical radiographic findings, a lack of classic granuloma formation in the late stages, and a negative TST. Delays in treatment may prove fatal.

Clinical aspects

A complex biological interplay occurs between M. tuberculosis and HIV in the co-infected host that results in the worsening of both pathologies. HIV promotes progression of M. tuberculosis latent infection to disease and, in turn, M. tuberculosis enhances HIV replication, accelerating the natural evolution of HIV infection.

Tuberculosis can appear at any stage of HIV infection, and its presentation varies with the stage. The clinical features of tuberculosis are closely related to the level of immune deficiency of the HIV-infected patient. In countries with a high prevalence of tuberculosis, tuberculosis is often a very early complication of HIV infection and often occurs when the level of cellular immunity is relatively high. It thus has the same aspects as among HIV-negative individuals.

At an early stage of immune deficiency, when the number of CD4 lymphocytes is greater than 200/mm^3, the clinical and radiographic features of pulmonary tuberculosis are similar to those in patients without HIV infection, with a predominance of smear-positive patients (75–85 %).Above this level, a complete TB granuloma is produced in response to M.tuberculosis infection, including multinucleated giant cells, macrophages, CD4+ and CD8+ Tlymphocytes and a central caseous necrosis. Pulmonary tuberculosis in such patients presents in a typical manner, with upper-lobe infiltrates and cavitation and without significant lymphadenopathy or pleural effusion.

At an advanced stage of immune deficiency, when the number of CD4+ lymphocytes is less than 200/mm^3, the formation of the granuloma is progressively impaired. Thus the appearance of tuberculosis changes from the typical, localized forms to the atypical, disseminated forms. In late stages of HIV infection, a primary tuberculosis–like pattern is more common. It is characterized by diffuse interstitial or miliary infiltrates, little or no cavitation,

associated with mediastinal lymphadenopathy and/or pleurisy. Overall, sputum smears may be positive less frequently among tuberculosis patients with HIV infection than among those without; thus, the diagnosis of tuberculosis may be unusually difficult, especially in view of the variety of HIV-related pulmonary conditions mimicking tuberculosis.

Extrapulmonary tuberculosis is common among HIV-infected patients. In various series, extrapulmonary tuberculosis — alone or in association with pulmonary disease - has been documented in 40–60 % of all cases in HIV–co-infected individuals. The most common extrapulmonary localizations of TB are serous effusions (pleurisy, pericarditis, ascites) and lymphadenopathy. Serous effusions (pleural, pericardial and/or peritoneal) are quite frequent in HIV/AIDS patients and may be caused by various other etiological agents. In TB pleurisy, the aspirated fluid is exudative with a predominance of lymphocytes. Pleural biopsy and mycobacterial culture of the fluid are the most useful and specific diagnostic tools. Adenosine deaminase (ADA) levels above 50 U/L in non-purulent pleural fluid specimens have a high positive predictive value for the diagnosis of TB.

Cervical lymphadenitis is the second most frequent extrapulmonary localization of TB in AIDS patients, after pleurisy. Aspiration puncture of a swollen and fluctuant lymphadenopathy usually yields a purulent or caseous material with abundant AFB on microscopy examination

Meningitis are also frequent, particularly in advanced HIV disease. Other organs may be involved, including the gastrointestinal tract, liver, kidneys, urinary tract, adrenal gland, larynx and genital (male and female) tract.

Course of tuberculosis

The course of tuberculosis under treatment in HIV-positive patients is similar to that observed in HIV-negative patients, if standardised short-course chemotherapy is applied. However, side-effects are more frequent. The risk of dying is still higher in HIV-infected patients. Much of this is due to other complications of HIV infection but some deaths seem directly due to tuberculosis. The long-term prognosis is therefore poor, as in all HIV-positive patients. But treatment of the patient's tuberculosis and antiretroviral drugs for HIV gives the patient a longer period of improved health. Moreover, anti-tuberculosis treatment stops the spread of tuberculosis to others. Unfortunately, tuberculosis seems to speed up the progress of the HIV illness. In addition to anti-tuberculosis treatment, antiretroviral treatment must thus be offered to all tuberculosis patients known to have HIV infection.

So, tuberculosis is a common complication of HIV infection. It can be the first sign of infection or it can occur in a subject known to be HIV-infected. Patients with HIV or AIDS who present with signs compatible with tuberculosis should undergo the same rigorous investigations as HIV-negative patients. The standardized chemotherapy regimens used for treating tuberculosis are as effective among HIV-positive as among HIV-negative patients; however, the fatality rate is higher among HIV-positive patients because of AIDS-related complications.

Immune reconstitution inflammatory syndrome

This syndrome, also known as IRIS, consists of a paradoxical worsening of clinical disease shortly after the initiation of drug treatment. Irrespective of the HIV status, the immune system is impaired in the advanced stages of TB as shown by low levels of circulating CD4+ T lymphocytes. Once the treatment starts to produce an effect, an «immune restoration» occurs that reflects the reconstituted immunity to M. tuberculosis. The syndrome includes an enlargement of the affected lymph nodes and of the lung lesions accompanied by an exacerbation of the general symptoms (fever and malaise and/or local reactions in lymph nodes, lungs, pleura and the central nervous system, depending on the localization of the TB lesions). This condition resolves spontaneously during the course of antituberculosis therapy.

Since the beginning of the highly active antiretroviral therapyera, the immune reconstitution inflammatory syndrome has been observed with increasing frequency. This syndrome is observed most frequently when the treatment of both infections is started in close temporal proximity. In AIDS patients, the immune reconstitution inflammatory reactions are best managed with anti-inflammatory agents, including corticosteroids such as prednisone 20-40 mg/d, if necessary. Both antituberculosis and antiretroviral therapy should be continued during the entire reconstitution syndrome.

Treatment of latent tuberculosis infection in HIV/AIDS patients

The classical method for detection of TB infection is the skin test reaction with PPD RT23 2 UT or PPDS 5 UT. In HIV-infected persons, a nodule of 5 mm or more is considered positive. Particularly in this population, the reliability of the method of detection of latent infection is highly dependent on the level of immunosuppression. Quantiferon is a whole blood assay for the detection of interferon gamma produced by peripheral lymphocytes in response to specific M. tuberculosis antigens. This test often yields negative or indeterminate results in severely immunosupressed AIDS patients. On the other hand, preliminary results in AIDS patients suggest that the performance of ELISPOT a test that enumerates Mycobacterium tuberculosis antigen-specific IFN-γ-secreting T cells test is not affected by HIV-associated immunosuppression.

When latent TB infection is detected in an HIV-positive person, he/she should receive chemoprophylaxis. The treatment consists of a course of at least six months:

— preferable nine months of INH. Alternatively, a four-month course of RIF may;

— be indicated. Both drugs are administered in their usual dosages.

The risk exists, however, of overlooking a sub-clinical TB, thus selecting INH resistant, or worse, RIF resistant mutants. A two-month course of treatment consisting of two drugs (RIF plus PZA) is expected to prevent the development of resistance, while the shor t-course treatment would grant a better adherence. The protective effect of a number of TB chemoprophylaxis regimens in HIV-positive, PPD-positive persons has been sufficiently proven.

7.2. Tuberculosis and maternity — clinical features of tuberculosis in pregnancy and the postpartum period. Diagnostic and treatment for tuberculosis during pregnancy and breast-feeding

Tuberculosis — high risk for mother and child. 2 times more possible premature birth, especially in patients from the group of social risk. Newborns are often sick. Children are born with low birth weight. Perhaps the progression of TB during pregnancy.

But pregnancy is not a high risk factor for TB. More susceptible women in the first trimester of pregnancy and after the abortion. The presence of TB in women is not an indication for termination of pregnancy. The most common forms of TB in pregnancy — pleurisy, infiltrative form, miliary tuberculosis.

The main method of detection of TB — sputum for MBT. X-ray examination is best done after 12 weeks of pregnancy in compliance with the safety precautions.

Pregnancy can't be a barrier for the treatment of TB. In untreated TB in the mother increases the risk of fetal infection (congenital TB). Together with isoniazid should be prescribed pyridoxine for the prevention of neurotoxicity. MDR-TB treatment with second-line anti-TB drugs start after the first trimester of pregnancy. Not prescribed to pregnant aminoglycosides, since they cross the placenta and cause fetal damage to the auditory nerve and kidney.

TB breastfeeding women should receive a full course of treatment. All anti-TB drugs are compatible with breastfeeding. TB patients with negative sputum smears can breastfeed. If sputum smears are positive, it is necessary to avoid close contact with the child to decide the problem of use infant formula.

7.3. Pulmonary tuberculosis associated with other lung diseases. TB in diabetes mellitus and chronic renal failure

Chronic bronchitis and COPD

Chronic bronchitis and COPD increase the risk of active TB disease and its unfavorable course. The reasons of that are defects in local defense factors of respiratory system, mucociliary clearance, insufficient aeration and perfusion of defective sections of lung tissue. Comorbidity makes difficult to diagnose TB which leads to late diagnosis. Patients and doctors evaluate increasing symptoms (cough, fever, dyspnea chest pain) as exacerbation of existing non-specific diseases. All patients with prolonged symptoms of intoxication and cough persisting for more than 3 weeks with sputum, hemoptysis or chest pain should be examined by sputum microscopy.

Diabetes mellitus

Before the advent of anti-tuberculosis chemotherapy and the generalized use of insulin therapy, the incidence and mortality rates of TB among patients with diabetes mellitus were high. In patients whose diabetes is difficult to control, the immune defects are presumably more severe, and pulmonary TB tends to be more aggressive producing cavities and extensive lesions in the lower third of the lungs.

The presence of diabetes mellitus may potentiate the adverse effects of anti-TB drugs, especially renal dysfunction and peripheral neuropathy. Diabetes must be managed closely throughout the treatment of DR-TB. The health-care provider should be in close communication with the physician who manages the patient's diabetes. Oral hypoglycaemic agents are not contraindicated during the treatment of DR-TB but may require the patient to increase the dosage. Use of ethionamide or protionamide may make it more difficult to control insulin levels. Creatinine and potassium levels should be monitored more frequently, often weekly for the first month and then at least monthly thereafter.

Renal insufficiency

In patients with chronic renal insufficiency, TB often has a slow onset with lowgrade fever, dry cough, dyspnea, pleuritis and/or pericarditis. TB occurs frequently in patients undergoing long periods of dialysis (on average, after 22 months), and extrapulmonary presentations (i. e. ganglionar) are common. As the mortality rate is high when the diagnosis is delayed, TB must always be considered a possibility, and appropriate invasive and non-invasive procedures should be employed to ensure an early diagnosis. As a rule, patients with *chronic renal failure* should not receive aminoglycosides and should receive ethambutol only if serum levels can be monitored. Isoniazid, rifampin, and pyrazinamide may be given in the usual doses in cases of mild to moderate renal failure, but the dosages of isoniazid and pyrazinamide should be reduced for all patients with severe renal failure except those undergoing hemodialysis.

Peptic ulcer disease

In patients with peptic ulcer disease — higher risk of developing TB. Frequent exacerbations and digestive disorders at peptic ulcer disease reduce the organism's resistance, promoting the development of TB.

TB in these patients tends to progression, the development chronic forms, long-term exacerbation. The simultaneous presence of two diseases adversely affects their course, there are often complications peptic ulcer disease, massive gastric bleeding, reduces the effectiveness of anti-TB treatment.

During exacerbation peptic ulcer disease anti-TB drugs designate parenterally in combination with anti-ulcer medication. After elimination of exacerbation back to give anti-TB drugs by the generally accepted methods.

Liver disorders

The first-line drugs isoniazid, rifampicin and pyrazinamide are all associated with hepatotoxicity. Of the three, rifampicin is least likely to cause hepatocellular damage, although it is associated with cholestatic jaundice. Pyrazinamide is the most hepatotoxic of the three first-line drugs. Among the second-line drugs, ethionamide, protionamide and PAS can also be hepatotoxic, although less so than any of the first-line drugs. Hepatitis occurs rarely with the fluoroquinolones.

Patients with a history of liver disease can receive the usual DR-TB chemotherapy regimens provided there is no clinical evidence of severe chronic liver disease, hepatitis virus carriage, recent history of acute hepatitis or excessive alcohol

consumption. However, hepatotoxic reactions to antituberculosis drugs may be more common in these patients and should be anticipated.

In general, patients with chronic liver disease should not receive pyrazinamide. All other drugs can be used, but close monitoring of liver enzymes is advised. If significant aggravation of liver inflammation occurs, the drugs responsible may have to be stopped.

Uncommonly, a patient with TB may have concurrent acute hepatitis that is unrelated to TB or antituberculosis treatment. In this case, clinical judgement is necessary. In some cases, it is possible to defer antituberculosis treatment until the acute hepatitis has been resolved. In other cases when it is necessary to treat DR-TB during acute hepatitis, the combination of four nonhepatotoxic drugs is the safest option.

Silicotuberculosis

Silicos is a form of pneumoconiosis. It results from inhalation of dust containing crystalline silica particles of size 0,5–5 microns in diameter. Prevalence of pulmonary TB in silicotics is more common when to prevalence in general population. This entity is called silicotuberculosis.

Silicotic workers have an approximately threefold greater risk of developing TB and a three- to fivefold greater risk of dying from TB than the general population and 20 to 25 % develop TB at some time in their working career or retirement. The association is dose-dependent, increasing with greater profusion of silicosis on chest radiograph, although the size of nodules and presence of progressive massive fibrosis might be more significant in determining the risk of TB.

Mechanisms underlying these associations are complex and not fully understood. However, alveolar macrophages are the first line of defence against mycobacteria and are also required to phagocytose and assist in the clearance of silica particles. The physicochemical properties of crystalline quartz result in damage to cell membranes through a variety of processes, leading to death, lysis and release of dust particles together with potentially tissue-damaging enzymes and other substances.

The onset of symptoms may be insidious, and general symptoms (fever, night sweats, muscle pain and fatigue) predominate. The presence of hemoptysis and increasing respiratory symptoms should alert to the possibility of TB. The presence of silicosis makes chest radiographic changes more difficult to interpret. Careful scrutiny for new changes, particularly the development of cavitation, poorly defined «fluffy» infiltrates surrounding previous tuberculous lesions and the appearance of new crops of poorly defined nodules should be performed. Sputum examination is mandatory and should be repeated in high-risk cases. Chest CT scans may help to define potential new areas of involvement, and serve as a guide to bronchoscopic examination and sampling. A high index of suspicion must be maintained in all silica-exposed and silicotic patients as TB is a frequent finding in postmortem examinations.

8. TREATMENT OF TUBERCULOSIS

8.1. Principles and aims of active TB treatment. First-line anti-TB drugs. Modes of action, dosages and side effects of first-line anti-TB drugs

The treatment of tuberculosis is based on two bacteriological considerations: the combination of drugs to avoid the selection of drug resistance, and the need for prolonged treatment to ensure that all bacteria in their different phases of metabolic growth are effectively destroyed.

The two aims of tuberculosis treatment are to interrupt tuberculosis transmission by rendering patients noninfectious and to prevent morbidity and death by curing patients with tuberculosis.

Drugs for treating TB are usually classified as first- and second-line drugs (5 groups).

Table 8.1 — Classification of anti-tuberculosis drugs

First-line	**Second-line**			
Isoniazid				
Rifampicin	**Injectable**			
Pyrazinamide	Kanamycin	**Quinolone**		
Ethambutol	Capreomycin	Ofloxacin	**Other 2nd line**	
Streptomycin*	Amikacin	Levofloxacin	Etionamide	**Other drugs**
		Moxifloxacin	Cycloserine	(unclearefficacy)
		Gatifloxacin	PAS	clofazimine
			Terisidone	linezolid
				amoxicillin/clavulanat
				thioacetazone
				clarithromycin
				imipenem

*Some reports include streptomycin among the second-line drugs, since its use has declined in recent years, due to the high rates of resistance

The appropriate treatment of tuberculosis is chemotherapy consisting of a combination of several anti-tuberculosis drugs. The duration of treatment lasts for 6–8 months and is known as «short-course chemotherapy».

There are five key (first-line) anti-tuberculosis drugs:

isoniazid
rifampicin
pyrazinamide
streptomycin
ethambutol

The use of any of these drugs as single preparations leads to the selection of naturally resistant strains that normally make up the bacterial populations. This is why several anti-tuberculosis drugs must be given together in order to achieve cure in a patient with tuberculosis.

Table 8.2 — Dosages of the essential anti-tuberculosis drugs

Anti-TB drugs	Mode of action	Daily treatment			
		Children in mg/kg (maximum)	Adults		
			Weight class		
			<33 kg, mg/kg	33–50 kg, mg per day	>50 kg mg per day
Isoniazid (H)	Bactericidal	10–15 (300)	4–6	200–300	300
Rifampicin (R)	Bactericidal	10–20 (600)	10–20	450–600	600
Pyrazinamide (Z)	Bactericidal	30–40 (2000)	30–40	1000–1750	1750–2000
Ethambutol (E)	Bacteriostatic	15–25 (1200)	15–25	800–1200	1200–1600
Streptomycin (S)	Bactericidal	20–40	15	0,5	1,0

Modes of action of anti-TB drugs

A population of TB bacilli in a TB patient consists of the following groups:

a) metabolically active, continuously growing bacilli inside cavities;

b) bacilli inside cells, e.g. macrophages;

c) semidormant bacilli (persisters), which undergo occasional spurts of metabolic activity;

d) dormant bacilli, which fade away and die on their own.

Different anti-TB drugs act against different groups of bacilli. Anti-TB drug treatment takes a long time because it is difficult to kill the semidormant TB bacilli.

Table 8.3 — Anti-TB drugs: mechanisms of action

Drug	Cellular function inhibited	Target
First-line drugs		
Isoniazid	Mycolic acid synthesis	Enoyl reductase
Rifampicin	RNA synthesis	RNA polymerase
Ethambutol	Arabinogalactan synthesis	Arabinosyl transferase
Pyrazinamide	Cell pH homeostasis*	
Second-line drugs		
Fluoroquinolone	DNA supercoiling	DNA gyrase
Ethionamide	Mycolic acid synthesis	Enoyl reductase
Streptomycin	Protein synthesis	30S ribosomal subunit
Kanamycin, Amikacin	Protein synthesis	30S ribosomal subunit
Capreomycin	Protein synthesis	30S/50S ribosomal subunit

*the mechanism of action remains to be not totally clear

Bacteriocidal drug

Isoniazid is a pro-drug that requires processing by the bacterial catalase-peroxidase to become active. Once activated, it inhibits the biosynthesis of mycolic acids, which are essential components of the mycobacterial cell wall. This drug is bactericidal against metabolically active bacilli and bacteriostatic against resting bacilli. Isoniazid is active against M. tuberculosis, M. bovis and M. kansasii. Isoniazid is readily absorbed from the gastrointestinal tract (although absorption is reduced by food) or following intramuscular injections. It diffuses in-

to all body tissues, including cerebrospinal fluid. The plasma half-life ranges from 1 to 6 hours. Isoniazid is metabolized in the liver and the small intestine. Within the population, there are two groups of patients, depending on whether INH is acetylated slowly or rapidly, a characteristic that is genetically determined. Plasma INH concentrations are lower in rapid acetylators than in slow acetylators, although this difference does not affect the efficacy of the treatment. INH and its metabolites are excreted in the urine.

Rifampicin can kill the semidormant bacilli that isoniazid cannot. It inhibits gene transcription, by interacting with the beta subunit of the RNA polymerase enzyme. It is bactericidal against dividing mycobacteria and also has some activity against non-dividing bacilli. This drug is readily absorbed from the gastrointestinal tract (food may delay or decrease rifampicin absorption). It also can be given intravenously. In blood, rifampicin is bound to plasma proteins, and distributes into body tissues and fluids, including cerebrospinal fluid and breast milk, and crosses the placenta. The half-life ofrifampicin ranges from 2 to 5 hours. Rifampicin is metabolized in the liver, and excreted in the bile, feces and urine.

Streptomycin inhibits protein synthesis in bacterial cell. Like most aminoglycosides, is poorly absorbed from the gastrointestinal tract, and therefore it must be administered by intramuscular injection. The half-life forstreptomycin is about 2.5 hours. Streptomycin and the other aminoglycosides diffuse well into most extracellular fluids. Streptomycin does not appear to be metabolized, and is excreted unchanged in the urine.

Pyrazinamide kills bacilli in an acid environment inside cells, e. g. macrophages. Pyrazinamide is known to be structural analogue of nicotinamide. Its mechanism of action remains to be not totally clear. Pyrazinamide is a prodrug that diffuses into M. tuberculosis, where the enzyme pyrazinamidase converts pyrazinamide to the active form pyrazinoic acid. Under acidic conditions, the pyrazinoic acid that slowly leaks out converts to the protonated conjugate acid, which is thought to diffuse easily back into the bacilli and accumulate. The net effect is that more pyrazinoic acid accumulates inside the bacillus at acid pH than at neutral pH.

Bacteriostatic drug

Ethambutol is only active against dividing mycobacteria, being bacteriostatic. Since ethambutol affects the biosynthesis of the cell wall, it has been suggested that it contributes towards increasing the susceptibility of M. tuberculosis to other drugs.Ethambutol is given orally, as it is well absorbed in the gastrointestinal tract (and not affected significantly by food), although a part is excreted in the feces. The half-life is about 3 to 4 hours. Only a fraction of ethambutol is metabolized in the liver; the unchanged drug and its metabolite+s are excreted in the urine.

Sterilizing action

This means killing all the bacilli. The persisters are hardest to kill. The aim of killing all the bacilli is to prevent relapse. Rifampicin is the most effective

sterilizing drug. Its effectiveness makes **short-course** chemotherapy possible. Pyrazinamide is also a good sterilizing drug, since it kills the bacilli protected inside cells.

Most TB patients complete their treatment without any significant drug side-effects. However, a few patients do develop side-effects. So clinical monitoring of all TB patients for side-effects is important during TB treatment.

Table 8.4 — Side-effects of anti-TB drugs

Drug	Common side-effects	Rare side-effects
Isoniazid (H)	— peripheral neuropathy — hepatitis if age > 40 — sleepiness/lethargy	convulsions, pellagra, joint pains, agranulocytosis, lupoid reactions, skin rash, acute psychosis
Rifampicin (R)	— gastrointestinal: anorexia, nausea, vomiting, abdominal pain, hepatitis — reduced effectiveness of oralcontraceptive pill	acute renal failure, shock, thrombocytopenia, skin rash, «flu syndrome» (intermittent doses), pseudomembranous colitis, pseudoadrenal crisis, osteomalacia, haemolytic anaemia
Pyrazinamide (Z)	— joint pains — hepatitis	gastrointestinal symptoms, skin rash, sideroblastic anaemia
Ethambutol (E)	— optic neuritis	skin rash, joint pains, peripheral neuropathy
Streptomycin (S)	— auditory and vestibular nerve damage (also to fetus) — renal damage	skin rash

Table 8.5 — Symptom-based approach to management of drug side-effects

Side-effects	Drug(s) probably responsible	Management
Minor		***Continue anti-TB drugs***
anorexia, nausea, abdominal pain	rifampicin	give tablets last thing at night
joint pains	pyrazinamide	give aspirin or nonsteroidal anti-inflammatory drug
burning sensation	isoniazid	give pyridoxine in feet 50–75 mg daily
orange/red urine	rifampicin	reassurance
Major		***Stop drug(s) responsible***
skin itching/rash	streptomycin	stop anti-TB drugs (see below)
deafness (no wax on auroscopy)	streptomycin	stop streptomycin, give ethambutol instead
dizziness (vertigo and nystagmus)	streptomycin	stop streptomycin, give ethambutol instead
jaundice (other causes excluded)	most anti-TB drugs	stop all anti-TB drugs until jaundice resolves (see below)
vomiting and confusion (suspected drug-induced pre-icteric hepatitis)	most anti-TB drugs	stop anti-TB drugs, urgent liver function tests
visual impairment	ethambutol	stop ethambutol
generalized, including shock and purpura	rifampicin	stop rifampicin

8.2. TB treatment regimens. Initial (intensive) phase and a continuation phase

Treatment regimens have an initial (intensive) phase and a continuation phase. The initial phase is designed for the rapid killing of actively growing bacilli and the killing of semidormant bacilli. This means a shorter duration of infectiousness. The continuation phase eliminates bacilli that are still multiplying and reduces failures and relapses. The principles of treatment are the same in all TB patients (adults and children).

There are several possible regimens. The regimen recommended depends on the patients diagnostic category.

Table 8.6 — Category of TB patient for registration on diagnosis

Diagnostic/registration category	Definition	
New	A patient who has definitely never taken anti-TB drugs or who has taken anti-TB drugs for less than one month.	
Re-treatment cases	Relapse	A TB patient who: a) previously received treatment and was declared cured or treatment completed; and b) has once again developed bacteriologically positive (by smear or culture) TB
	Treatment after failure	A patient who is started on a re-treatment regimen after having failed previous treatment.
	Treatment after default	A TB patient who returns to treatment, bacteriologically positive, following interruption of treatment for 2 months or more.
Transfer in	A TB patient who has been transferred from another TB register to continue treatment.	
Other	All TB patients who do not fit the above definitions. This group includes chronic cases (TB patients who are sputum smear-positive at the end of a re-treatment regimen).	

Based on case definition, all TB patients (adults and children) fall into one of four diagnostic categories for treatment.

Table 8.7 — Recommended treatment regimens for each diagnostic category

TB diagnostic category	TB patients	TB treatment regimens	
		Initial phase	Continuation phase
I	New smear-positivepatients. New smear-negativepulmonary TB withextensive parenchymalinvolvement. Severe concomitant HIV disease or severe forms of extrapulmonary TB.	**2HRZE**	**4HR or 6HE**
II	Previously treatedsputum smear-positivepulmonary TB:	**2HRZES/1HRZE**	**5HRE**

	— relapse — treatment after default — treatment failure		
III	New smear-negativepulmonary TB (other than in Category I). Less severe forms of extrapulmonary TB.	**2HRZE**	**4HR or 6HE**
IV	Chronic and MDR-TB cases (still sputum-positive after supervised re-treatment)	Specially designed individualized or standardized regimens are suggested for this category	

Use of TB drugs in children

The treatment regimens and drug dosages in mg/kg of body weight are the same for children as for adults. Children usually tolerate TB drugs very well and serious side-effects are unusual. Do not give thioacetazone to HIV-infected children. Ethambutol is safe even in children too young to report early visual side-effects provided that the recommended dose is not exceeded. Since TB drugs are often not available in syrup form, give children portions of tablets according to weight.

8.3. Preventing drug resistance. Second-line anti-TB drugs.Principles of DR-TB treatment.

Preventing drug resistance

A population of TB bacilli never previously exposed to anti-TB drugs will include a few naturally occurring drug-resistant mutant bacilli. Faced with anti-TB drugs, these drug-resistant mutant bacilli will grow and replace the drug-sensitive bacilli under the following circumstances:

a) inadequate anti-TB drug combinations;

b) inadequate application of anti-TB drug treatment.

Isoniazid and rifampicin are most effective in preventing resistance to other drugs. Streptomycin and ethambutol are slightly less effective.

Any patient with chronic or DR-TB requiring treatment with second-line drugs falls under WHO diagnostic category IV and will require specialized regimens.

Table 8.8 — Common treatment strategies for DR-TB

Standardizedtreatment	Representative DRS data in well-defined patient populations are used to design the regimen. All patients in a patient group or category receive the same regimen
Standardized treatment followed by individualized treatment	Initially, all patients in a certain group receive the same regimen based on DST survey data from representative populations. The regimen is adjusted when DST results become available (often DST is only done to a limited number of drugs)
Empirical treatment followed by individualized treatment	Each regimen is individually designed on the basis of patient history and then adjusted when DST results become available (often the DST is done of both first- and second-line drugs)

Designing a treatment regimen

- Regimens should be based on the history of drugs taken by the patient.
- Regimens should consist of at least four drugs with either certain, or almost certain, effectiveness.

- The drug dosage should be determined by body weight.
- An injectable agent (an aminoglycoside or capreomycin) is used for a minimum of six months and at least four months past culture conversion.
- The minimum length of treatment is 18 months after culture conversion.
- Each dose is given as directly observed therapy (DOT) throughout the treatment. A treatment card is marked for each observed dose.

Drugs for treating TB are usually classified as first- and second-line drugs (5 groups). This classification use a group system based on efficacy, experience of use and drug class (table 8–1).

8.4. Adjunctive therapy, surgical treatment of TB — indications and contraindications.

Deciding on other treatment measures

Apart from chemotherapy, which is necessary for treating all cases of tuberculosis, adjunctive therapy is indicated for certain sites.

Treatment with corticosteroids

The addition of corticosteroids at a dose of 0,5 mg/kg per day for 3 to 6 weeks has been shown to have an impact in the following cases:

1. Tuberculous meningitis of moderate severity, in order to improve neurological outcome and reduce fatality.
2. Tuberculous pericarditis, in order to reduce the need for surgical intervention and reduce fatality.

In pulmonary tuberculosis, tuberculous pleurisy and primary tuberculosis with lymphadenopathy, while treatment with corticosteroids may have short-term effects on symptoms and signs, has no long-term benefits.

Surgical treatment

During the first half of XX century, the finding that *Mycobacterium tuberculosis* was an obligate aerobe led to rapid growth of thoracic surgical operation: thoracoplasty, induced pneumothorax, plombage, and phrenic nerve crushing. Developed in the 1960 s, Rifampicin and other anti-TB drugs radically transformed the prognosis of the disease and limited the indications for surgical intervention. During the second part of XX century surgery was not a routine method of treatment but it was considered to be indicated for removing a pocket of bacteria that cannot be killed with long-term medicine treatment (persistent cavity, tuberculoma).

Radical surgical procedures are:

- pneumonectomy
- lobectomy
- segmental resection

Nowadays, the role of surgery in managing TB is enlarging due to the overall increase in global incidence, and the emergence of multidrug-resistant TB or extensive drug-resistant TB. Currently, thoracic surgery offers highly effective treatment of TB and its sequel with less trauma and morbidity than ever before. The advantage of Minimally Invasive Thoracic Surgery allows a wider range of TB patients to be considered for effective surgical management.

Currently, the surgical indications in pulmonary TB are:

- TB complications (e. g., hemoptysis, empyema, cavity formation associated with aspergilloma, adenopathy with fistula, bronchial stenosis);
- cases displaying an inappropriate healing response to medication, in which clinical and radiological pictures remain unchanged or indicate progression (e. g., cavity, tuberculoma);
- acid-fast bacilli sputum smears positivity after 3-month treatment period, with a circumscribed radiological lesion or a destroyed lung;
- previous relapse(s) in patients with histories of TB and proper drug regimen.

Indications for surgery in MDR-TB

- Localized disease.
- Persistent cavitary disease.
- Persistent sputum positivity MDR-TB with destroyed lobe of lung.

8.5. Monitoring of TB patients during treatment

All patients should be monitored to assess their response to therapy. Regular monitoring of patients also facilitates treatment completion and allows the identification and management of adverse drug reactions. All patients, their treatment supporters and health workers should be instructed to report the persistence or reappearance of symptoms of TB (including weight loss), symptoms of adverse drug reactions, or treatment interruptions.

Patient weight should be monitored each month, and dosages should be adjusted if weight changes.

A written record of all medications given, bacteriological response and adverse reactions should be maintained for every patients on the TB Treatment Card

Table 8.9 — Monitoring of patients with sputum smear-positive PTB

When to monitor	8-month treatment regimen	6-month treatment regimen
At time of diagnosis	sputum smear	sputum smear
At end of initial phase	sputum smear	sputum smear
In continuation phase	sputum smear(month 5)	sputum smear(month 5)
During last month of treatment	sputum smear(month 8)	sputum smear(month 6)

Sputum smear at end of initial phase

The vast majority of patients have a negative sputum smear at the end of the initial phase. If the sputum smear is still positive at the end of the initial phase, continue initial phase treatment with the same 4 drugs for 4 more weeks. If you check the sputum smear again at this point, it is unlikely still to be positive. Go on to the continuation phase (even if the sputum smear after the extra 4 weeks of initial phase treatment is still positive).

Sputum smear in continuation phase

In 8-month regimens, a positive sputum smear at 5 months (or any time after 5 months) means treatment failure. In 6-month regimens, a positive sputum smear at 5 months (or any time after 5 months) means treatment failure. A common cause of treatment failure is the failure of the program to ensure patient adherence to

treatment. The patient's treatment category changes to Category 2 and the re-treatment regimen starts.

Sputum smear on completion of treatment

Negative sputum smears in the last month of treatment and on at least one previous occasion mean bacteriological cure.

Table 8.10 — Recording treatment outcome

Cure	patient who is sputum smear-negative in the last month of treatment and on at least one previous occasion
Treatment completed	patient who has completed treatment but does not meet the criteria to be classified as a cure or a failure
Treatment failure	patient who is sputum smear-positive at 5 months or later during treatment
Died	patient who dies for any reason during the course of treatment
Defaulted (treatment interrupted)	patient whose treatment was interrupted for 2 consecutive months or more
Transferred out	patient who has been transferred to another recording and reporting unit and for whom the treatment outcome is not known

Pulmonary TB patients whose sputum smear microscopy was negative (or not done) before treatment and whose sputum smears are negative at 2 months need no further sputum monitoring. They should be monitored clinically; body weight is a useful progress indicator.

9. DIFFERENTIAL DIAGNOSIS FOR PRIMARY TUBERCULOSIS

9.1. General principles of differential diagnostic for pulmonary TB.

The symptoms started less than 3 weeks ago

These are more commonly indicative of acute respiratory infections, although tuberculosis remains a possibility. A history of an epidemic of acute respiratory illness in the community is especially important in such cases.

Diagnostic evaluation may reveal the following:

- inflammatory conditions of the respiratory tract, such as sore throat or acute bronchitis
- acute bacterial pneumonia, with pain in the side, high fever and evidence of pulmonary consolidation
- interstitial pneumonia, generally viral, with fever and dyspnoea
- more rarely, a lung abscess with fever and abundant purulent sputum

With appropriate treatment, including appropriate antibiotics (where indicated), symptoms will disappear within 1–2 weeks.

The symptoms have been present for more than 3 weeks

They can be more probably due to tuberculosis. However, symptoms that have been present for a very long time (several months or years), with a recent exacerbation that has prompted the consultation, suggest a chronic respiratory condition, although tuberculosis remains a possibility:

• Bronchiectasis with episodes of acute infection (a complication of previous tuberculosis or other respiratory infection). Abundant mucopurulent sputum and bacteriological examinations that are consistently negative for tuberculosis are characteristic of this condition.

• Chronic bronchitis or chronic obstructive pulmonary disease: the patient has had cough and sputum production each winter for at least 2 years. Seasonal episodes caused by acute infection are common. Gradually worsening breathlessness on effort is a symptom that may worry the patient. A history of tobacco smoking in individuals aged over 50 years or exposure to smoke from wood-fired cooking or heating in an unventilated room supports this diagnosis.

• Asthma may present with chronic symptoms. Episodic breathlessness, often occurring at night, and wheezing, alternating with periods of absence of symptoms, is suggestive of asthma. When the patient presents with such symptoms, peak flow measurement can demonstrate the presence of airflow obstruction that may be relieved by treatment with aerosol bronchodilators (such as salbutamol).

Other, less common conditions should also be considered in such cases:

• Mitral stenosis may present with episodes of breathlessness, accompanied by repeated light hemoptysis. Presence of the characteristic diastolic murmur can identify this condition.

• Heart failure with breathlessness, disseminated pulmonary râles and oedema in the legs.

• Lung cancer in men aged over 50 years with a long history of tobacco smoking presenting with cough, hemoptysis and sometimes persistent chest pain.

• Pneumoconiosis in the case of long-term exposure to mineral dusts.

The duration of symptoms in tuberculosis cases is shorter than that of chronic conditions and longer than that of acute conditions.

9.2. Mediastinal lymphadenopathy diseases — lymphogranulomatosis (Hodgkin lymphoma), lymphoma, thymus hiperplazia.

Hodgkin's Lymphoma (Hodgkin's disease, lymphogranulomatosis) is a cancer of the lymphatic system that is marked by the presence of a type of cell called the Reed-Sternberg cell. Lymphomas that do not contain Reed-Sternberg cells are classified under the heading of «non-Hodgkin's lymphomas».

The cause of Hodgkin's lymphoma is still uncertain and being researched. There is very persuasive evidence that at least some cases are associated with specific virus infections: the Epstein-Barr virus the Measles virus.

This disease is characterized by progressive enlargement of the lymph nodes, liver and spleen, also accompanied by progressive anemia. The symptom that most people notice first is swollen lymph nodes. Here are some of the more common signs and symptoms:

• swollen lymph nodes in the neck, armpit, or groin area that don't go away;
• unexplained fever;
• night sweats;
• weight loss over several months;
• tiredness and weakness;

- coughing or breathlessness;
- itch all over the body.

Non-Hodgkin lymphoma is a common term for large group of cancers of lymphocytes. Non-Hodgkin lymphomas can occur at any age and are often marked by lymph nodes that are larger than normal, fever, and weight loss. There are many different types of non-Hodgkin lymphoma. These types can be divided into aggressive (fast-growing) and indolent (slow-growing) types, and they can be formed from either B-cells or T-cells. B-cell non-Hodgkin lymphomas include Burkitt lymphoma, chronic lymphocytic leukemia/small lymphocytic lymphoma, diffuse large B-cell lymphoma, follicular lymphoma, immunoblastic large cell lymphoma, precursor B-lymphoblastic lymphoma, and mantle cell lymphoma. T-cell non-Hodgkin lymphomas include mycosis fungoides, anaplastic large cell lymphoma, and precursor T-lymphoblastic lymphoma. Lymphomas that occur after bone marrow or stem cell transplantation are usually B-cell non-Hodgkin lymphomas. Prognosis and treatment depend on the stage and type of disease.

Thymoma is an epithelial tumor of thymus.Some data suggest that Epstein-Barr virus may be associated with thymomas. The molecular pathogenesis remains undefined. It is most common in the fifth and sixth decades, are uncommon in children, and are distributed evenly between men and women. About 40–50 % of patients are asymptomatic; masses are detected incidentally on routine chest radiographs. When symptomatic, patients may have cough, chest pain, dyspnea, fever, wheezing, fatigue, weight loss, night sweats, or anorexia. Occasionally, thymomas may obstruct the superior vena cava.

9.3. Diagnostic approach to mediastinum lymphadenopathy diseases. Radiographic and laboratory features.

The staging evaluation for a patient with mediastinal lymphadenopathy diseases would typically include a careful history and physical examination; complete blood count; erythrocyte sedimentation rate; serum chemistry studies; chest radiograph; CT scan of the chest, abdomen, and pelvis. The diagnosis is confirmed by a biopsy.

Once a mediastinal mass is detected, a surgical procedure is required for definitive diagnosis. An initial mediastinoscopy or limited thoracotomy can be undertaken to get sufficient tissue to make an accurate diagnosis. Fine-needle aspiration is poor at distinguishing between lymphomas and thymomas but is more reliable in diagnosing germ cell tumors and metastatic carcinoma. Thymomas and lymphomas require sufficient tissue to examine the tumor architecture to assure an accurate diagnosis and obtain prognostic information.

Table 9.1 — Mediastinal lymphadenopathy diseases

Signs	Tuberculosis	Lymphomas	Thymoma
Risk factors	Contact with active TB patient HIV Diabetes mellitus Social risk factors	Epstein-Barr and some others virus infections	Epstein-Barr virus infections

Signs	Tuberculosis	Lymphomas	Thymoma
Symptoms	Asymptomatic in the majority of cases. Subtle generalized symptoms Mucocutaneous manifestations, although infrequent, are highly characteristic.	Mediastinal and perifericial lymphadenopathy	Often asymptomatic
Chest X-ray and CT	Typical primary complex, In some cases isolated mediastinal lymphadenopathy	Mediastinal lymph nodes enlargement, accompanied or not with lung dissemination.	Mediastinal mass in anterior mediasinum
Laboratory tests	Positive TST/IGRAs MBT positive sputum	High blood lymphocitosis	ESR increasing
Biopsy	TB granulomas with central caseoution, multinucleated giant cells and often the presence of tubercle bacilli.	Lymph cells neoplastic granulomas (with Reed-Sternberg cells in Hodgkin's lymphoma)	Neoplastic transformation of thymus epitelium

9.4. Sarcoidosis — definition, pathogenesis and morphology, classification, clinical variants, diagnostic and treatment.

Sarcoidosis is a disorder resulting in noncaseating granulomas in one or more organs and tissues; etiology is unknown. The lungs and lymphatic system are most often affected, but sarcoidosis may affect any organ.

Sarcoidosis affects mostly people aged 20 to 40 but occasionally affects children and older adults. Worldwide, prevalence is greatest in black Americans and northern Europeans, especially Scandinavians. Sarcoidosis is slightly more prevalent in women. The incidence increases in winter and early spring for unknown reasons.

Löfgren's syndrome: Löfgren's syndrome is a type of acute sarcoidosis that manifests as a triad of acute polyarthritis, erythema nodosum, and hilar adenopathy. It has distinct features, including fever, malaise, joint disease, and sometimes uveitis and parotitis. It is more common among Scandinavian and Irish women.

Löfgren's syndrome is often self-limited. Patients usually respond to NSAIDs. Rate of relapse is low.

Etiology

Sarcoidosis is thought to be due to an inflammatory response to environmental exposure in a genetically susceptible person. Proposed triggers include

- Viral, bacterial, and mycobacterial infections
- Inhalation of various agents: inorganic (eg, aluminum, zirconium, talc) or organic (eg, pine tree pollen, clay)

Pathophysiology

The unknown antigen triggers a cell-mediated immune response that is characterized by the accumulation of T lymphocytes and macrophages, release

of cytokines and chemokines, and organization of responding cells into granulomas. Clusters of disease in families and communities suggest a genetic predisposition, shared exposures, or, less likely, person-to-person transmission.

The result of the inflammatory process is formation of noncaseating granulomas, the pathologic hallmark of sarcoidosis. Granulomas are collections of mononuclear cells and macrophages that are differentiated into epithelioid and multinucleated giant cells, surrounded by lymphocytes, plasma cells, mast cells, fibroblasts, and collagen. Granulomas occur most commonly in the lung and lymph nodes but can involve the liver, spleen, eyes, sinuses, skin, bones, joints, skeletal muscle, kidneys, reproductive organs, heart, salivary glands, and nervous system. Granulomas in the lungs are distributed along lymphatics, with most occurring in peribronchiolar, subpleural, and perilobular regions.

Symptoms and Signs

Symptoms and signs depend on the site and degree of involvement and vary over time, ranging from spontaneous remission to chronic indolent illness. Accordingly, frequent reassessment for new symptoms in different organs is needed. Most cases are probably asymptomatic and thus go undetected. Pulmonary disease occurs in > 90 % of adult patients.

Symptoms and signs may include dyspnea, cough, chest discomfort, and crackles. Fatigue, malaise, weakness, anorexia, weight loss, and low-grade fever are also common; sarcoidosis is an unusual cause of fever of unknown origin. Nontender lymphadenopathy is often the only sign. Systemic involvement causes various symptoms, which vary by race, sex, and age. Women are more likely to have erythema nodosum and eye or nervous system involvement. Men and older patients are more likely to be hypercalcemic.

Diagnosis

- Chest imaging
- Biopsy
- Exclusion of other granulomatous disorders

Sarcoidosis is most often suspected when hilar adenopathy is incidentally detected on chest x-ray. These changes are the most common abnormality, and the x-ray appearance is roughly predictive of the likelihood of spontaneous remission in patients with pulmonary involvement. Therefore, if sarcoidosis is suspected, a chest x-ray should be the first test if it has not already been done.

A normal chest x-ray generally excludes the diagnosis; however, high-resolution CT may be indicated if sarcoidosis is strongly suspected because CT is more sensitive for detecting hilar and mediastinal lymphadenopathy. CT findings in more advanced stages (II to IV) include thickening of the bronchovascular bundles and bronchial walls; beading of the interlobular septa; ground-glass opacification; parenchymal nodules, cysts, or cavities; and traction bronchiectasis.

When imaging suggests sarcoidosis, the diagnosis is confirmed by demonstration of noncaseating granulomas on biopsy and exclusion of alternative causes of granulomatous disease.

The diagnostic evaluation, therefore, requires the following:

- Selection of a biopsy site.
- Exclusion of other causes of granulomatous disease.
- Assessment of the severity and extent of disease to determine whether therapy is indicated.

Sites for biopsy: Appropriate biopsy sites may be obvious from physical examination and initial assessment; peripheral lymph nodes, skin lesions, and conjunctivae are all easily accessible. However, bronchoscopic transbronchial biopsy is the diagnostic procedure of choice in patients with intrathoracic involvement because sensitivity is as high as 90 % when an experienced clinician does the procedure. Video-assisted thoracoscopy can provide access to lung tissue when bronchoscopic transbronchial biopsy is nondiagnostic. Mediastinoscopy is sometimes done when hilar or mediastinal lymphadenopathy exists in the absence of pulmonary infiltrates, especially if lymphoma is in the differential diagnosis. However, even in patients with only mediastinal adenopathy on x-ray or CT, transbronchial biopsies are often diagnostic. Open lung biopsy provides another way to obtain tissue but requires general anesthesia and is now rarely necessary. Clinical and x-ray findings may be accurate enough for diagnosis in stage I disease or in stage II disease when biopsy is not possible.

Exclusion of other diagnoses: Exclusion of other diagnoses is critical, especially when symptoms and x-ray signs are minimal, because many other disorders and processes can cause granulomatous inflammation. Biopsy tissue should be cultured for fungi and mycobacteria. Exposure history to occupational (silicates, beryllium), environmental (moldy hay, birds, and other antigenic triggers of hypersensitivity pneumonitis), and infectious (TB, coccidioidomycosis, histoplasmosis) antigens should be explored. PPD skin testing should be done early in the assessment along with anergy controls.

Disease severity assessment: Severity is assessed with

- Pulmonary function tests.
- Exercise pulse oximetry.

Pulmonary function test results are often normal in early stages but demonstrate restriction and reduced diffusing capacity for carbon monoxide (DLco) in advanced disease. Airflow obstruction also occurs and may suggest involvement of the bronchial mucosae. Pulse oximetry is often normal when measured at rest but may show effort desaturation with more extensive lung involvement. ABG analysis at rest and during exercise is more sensitive than pulse oximetry.

Recommended screening tests for extrapulmonary disease include

- ECG.
- Slit-lamp ophthalmologic examination.
- Routine blood tests to evaluate renal and hepatic function.
- Serum Ca levels.

Echocardiography, neuroimaging, lumbar puncture, bone x-rays or MRI, and electromyography may be appropriate when symptoms suggest cardiac,

neurologic, or rheumatologic disorders. Abdominal CT with radiopaque dye is not routinely recommended but can provide evidence of hepatic or splenic involvement (eg, enlargement, hypolucent lesions).

Laboratory testing plays an adjunctive role in establishing the diagnosis and extent of organ involvement. CBC may show anemia, eosinophilia, or leukopenia. Serum Ca may be elevated because vitamin D analogs are produced by activated macrophages. Blood urea nitrogen, creatinine, and liver function test results may be elevated in renal and hepatic sarcoidosis. Total protein may be elevated because of hypergammaglobulinemia. Elevated ESR is common but nonspecific. Measurement of Ca in a urine specimen collected over 24 h is recommended to exclude hypercalciuria, even in patients with normal serum Ca levels. Elevated serum ACE levels also suggest sarcoidosis but are nonspecific and may be low in patients taking ACE inhibitors or elevated in patients with various other conditions (eg, hyperthyroidism, Gaucher's disease, silicosis, mycobacterial disease, hypersensitivity pneumonitis). However, ACE levels may be useful for monitoring disease activity and therapeutic response in patients with confirmed sarcoidosis. Increased ACE levels in CSF may be useful for diagnosing CNS sarcoidosis.

Other adjunctive tests include bronchoalveolar lavage (BAL) and gallium scanning. BAL is used to help exclude other forms of interstitial lung disease if the diagnosis of sarcoidosis is in doubt and to rule out infection. The findings on BAL vary considerably, but lymphocytosis (lymphocytes >10 %), a CD4+/CD8+ ratio of > 3,5 in the lavage fluid cell differential, or both suggest the diagnosis in the proper clinical context. However, absence of these findings does not exclude sarcoidosis.

Whole-body gallium scanning may provide useful supportive evidence in the absence of tissue confirmation. Symmetric increased uptake in mediastinal and hilar nodes (lambda sign) and in lacrimal, parotid, and salivary glands (panda sign) are patterns highly suggestive of sarcoidosis. A negative result in patients taking prednisone is unreliable.

Prognosis

Although spontaneous improvement is common, the manifestations of the disorder and its severity are highly variable, and many patients require corticosteroids some time during the course of their disease. Thus, serial monitoring for evidence of relapse is imperative. In about 90 % of patients who have spontaneous remission, remission occurs within the first 2 years after diagnosis;<10 % of these patients have relapses after 2 years. Patients who do not experience remission within 2 years are likely to have chronic disease.

Sarcoidosis is thought to be chronic in up to 30 % of patients, and 10 to 20 % experience permanent sequelae. The disease is fatal in 1 to 5 % of patients, typically due to respiratory failure caused by pulmonary fibrosis, and less often due to pulmonary hemorrhage caused by aspergilloma. However, in Japan, infiltrative cardiomyopathy causing heart failure and arrhythmias is the most common cause of death.

Prognosis is worse for patients with extrapulmonary sarcoidosis and for blacks. Recovery occurs in 89 % of whites and 76 % of blacks with no extrathoracic disease and in 70 % of whites and 46 % of blacks with extrathoracic disease.

Good prognostic signsinclude

- Erythema nodosum.
- Acute arthritis.

Poor prognostic signsinclude

- Uveitis.
- Lupus pernio.
- Chronic hypercalcemia.
- Neurosarcoidosis.
- Nephrocalcinosis.
- Myocardial disease.
- Extensive pulmonary involvement.

Little difference is demonstrable in long-term outcome between treated and untreated patients, and relapse is common when treatment ends.

Treatment

- Sometimes corticosteroids.
- Rarely immunosuppressants.

Because sarcoidosis often spontaneously resolves, asymptomatic patients and patients with mild symptoms do not require treatment, although they should be monitored for signs of deterioration. These patients can be followed with serial x-rays, pulmonary function tests (including diffusing capacity), and markers of extrathoracic involvement (eg, routine renal and liver function testing). Patients who require treatment regardless of stage include those with the following:

- Worsening symptoms.
- Limitation of activity.
- Markedly abnormal or deteriorating lung function.
- Worrisome x-ray changes (cavitation, fibrosis, conglomerate masses, signs of pulmonary hypertension).
- Heart, nervous system, or eye involvement.
- Renal or hepatic insufficiency or failure.
- Disfiguring skin or joint disease.

Treatment is with corticosteroids. A standard protocol is prednisone 0.3 to 1 mg/kg po once/day depending on symptoms and severity of findings. Alternate-day regimens are also used: eg, prednisone 40 to 60 mg po once every other day. Although patients rarely require > 40 mg/day, higher doses may be needed to reduce complications in patients with ocular, myocardial, or neurologic disease. Response usually occurs within 2 to 4 wk, so symptoms and results of chest x-ray and pulmonary function tests may be reassessed between 4 and 12 wk. Chronic, insidious cases may respond more slowly. Corticosteroids are tapered to a maintenance dose (eg, prednisone ≤ 10 mg every other day if possible) after

evidence of response and are continued for a minimum of 12 mo if improvement occurs. The optimal duration of treatment is unknown. Premature taper can result in relapse. The drug is slowly stopped if response is absent or equivocal. Corticosteroids can ultimately be stopped in most patients, but because relapse occurs up to 50 % of the time, monitoring should be repeated, usually every 3 to 6 mo. Corticosteroid treatment should be resumed for recurrence of symptoms and signs, including dyspnea, arthralgia, fever, hepatic insufficiency, cardiac arrhythmia, CNS involvement, hypercalcemia, ocular disease uncontrolled by local drugs, and disfiguring skin lesions.

Data on use of inhaled corticosteroids for pulmonary sarcoidosis are not definitive, but some evidence suggests that this route of administration can relieve cough in patients with endobronchial involvement. Topical corticosteroids may be useful in some cases of dermatologic and ocular disease.

About 10 % of patients requiring therapy are unresponsive to tolerable doses of a corticosteroid and should be given a 6-mo trial of methotrexate starting at 2,5 mg po once/wk and increasing in increments of 2,5 mg /wk to a total of 10 to 15 mg/wk as tolerated to keep the WBC count > 3000/μL. Initially, methotrexate and corticosteroids are both given; over 8 wk, the corticosteroid dose can be tapered and, in many cases, stopped. The maximal response to methotrexate, however, may take 6 to 12 mo. In such cases, prednisone must be tapered more slowly. Serial blood counts and liver enzyme tests should be done every 1 to 2 wk initially and then every 4 to 6 wk once a stable dose is achieved. Folate (1 mg po once/day) is recommended for patients treated with methotrexate.

Other drugs reported to be effective in small numbers of patients who are corticosteroid-resistant or who experience complicating adverse effects include azathioprine cyclophosphamide, chlorambucil, chloroquine or hydroxychloroquine, thalidomide, pentoxifylline, and infliximab.

Hydroxychloroquine 200 mg po bid to tid can be as effective as corticosteroids for treating hypercalcemia or disfiguring skin sarcoidosis. Although immunosuppressants are often more effective in refractory cases, relapse is common after cessation.

Lung transplantation is an option for patients with end-stage pulmonary involvement, although disease may recur in the transplanted organ.

10. DIFFERENTIAL DIAGNOSIS FOR SECONDARY TB

X-ray appearance of secondary tuberculosis as well as most of lung disease is not specific. Lung dissemination and infiltrates can present more then 20 nosologies. As a rule there are no specific clinical signs to differentiate thus verification requires complex data estimation including risk factors, symptoms and history, chest X-ray and CT, laboratory tests with compulsory sputum investigation. Dynamic and response to treatment often have a great value. Large portion of lung dissemination requires biopsy for verification. Diagnostic approach for most common nosologies is presented in the tables.

Table 10.1 — Differential diagnosis for lung dissemination

Signs	Tuberculosis	Pneumonia	Metastatic cancer	Sarcoidosis	Pneumoconiosis	Interstitial lung disease
Risk factors	Contact with active TB patient HIV Other medical and social risk factors	Getting cold Contact with contagious patients	Most common primaries: breast, colorectal and renal carcinoma	Not defined	Occupational history with inhaling dust over a long period of time	Not defined
Symptoms	Respiratory symptoms and intoxication longer than 3 weeks	Acute onset Respiratory syndrome accompanied with intoxication	Often asymptomatic	Often asymptomatic Breath restrictive syndrome in extended forms	Gradually progressing breath restrictive syndrome	Severe breath restrictive syndrome
Chest X-ray and CT	Predominantly upper and middle areas Often accompanied with cavitation Milletlike total dissemination in miliary TB	Predominantly middle and lower areas	Peripheral, rounded nodules of variable size, scattered throughout both lungs	Bihilar lymphadenopathy and reticulonodular infiltrates	Gradually progressing (years) dissemination, first in middle areas then total	Linear or reticular opacities Small nodules Honeycombing Ground glass opacities Thickened alveolar septa
Laboratory tests	MBT + sputum	Gram-positive/ negative bacteria in sputum (S pneumonia up to 80 %) Blood leukocytosis	ERS increasing Atypical cells in sputum	Mainly normal	Mainly normal	ERS increasing Bronchoalveolar lavage fluid contains up to 20 % eosinophils
Biopsy	TB granuloma	Not indicated	Neoplasia	Sarcoidosis granuloma	Typical noddles accompanied with fibrosis	Depending on nosology
Diagnostic approach	Reiterated sputum investigation for MBT	Estimating respond to antibiotic, clinical and X-ray dynamic within 2–3 weeks	Verification by biopsy	Verification by biopsy	Estimating occupational history Regular sputum investigation for MBT	Verification by biopsy

Table 10.2 — Differential diagnosis for lung infiltrates (pneumonia, lung cancer, pulmonary eosinophilic infiltrates)

Signs	Tuberculosis	Pneumonia	Lung cancer	Pulmonary eosinophilic infiltrates
Risk factors	Contact with active TB patient HIV Other medical and social risk factors	Getting cold Contact with contagious patients	Smoking Elder age Male	Allergy of different types
Symptoms	Often asymptomatic or subclinical Respiratory symptoms have been present for more than 3 weeks	Acute onset Respiratory syndrome accompanied with intoxication	Asymptomatic on early stage Coughing, lung hemorrhage,weight loss Superior vena cava obstruction	Often asymptomatic
Chest X-ray and CT	Predominantly upper areas Often accompanied with cavitation and contralateral dissemination.	Segmental or lobal shadows	Mass, widening of the mediastinum (suggestive of spread to lymph nodes there), atelectasis (collapse) Solitary nodule	Transient migratory infiltrates
Laboratory tests	MBT + sputum	Gram-positive/negative bacteria in sputum (S. pneumonia up to 80 %) Blood leukocytosis	ERS increasing Atypical cells in sputum	Elevated peripheral eosinophil count
Biopsy	TB granuloma	Not indicated	Neoplasia	Not indicated
Diagnostic approach	Reiterated sputum investigation for MBT	Estimating respond to antibiotic, clinical and X-ray dynamic within 2–3 weeks	Verification by biopsy	Control X-ray if asymptomatic infiltrates accompanied by elevated peripheral eosinophil count are found

10.3. Differential diagnosis for lung cavities (lung abscess and necrotizing pneumonia, bullous emphysema, cystic lung disease, lung malformation,)

Cavities are frequent manifestations of a wide variety of pathological processes involving the lung. The radiographic appearance of cavitary lesions can sometimes be useful to differentiate among a broad spectrum of etiologies but should be combined with clinical and laboratory data to obtain an accurate diagnosis. One traditional method used to classify cavitary lesions is wall thickness. Cavitary lesions associated with specific diseases are frequently described as being «thick walled» or «thin walled», but exact definitions for these terms are often lacking. Radiographic studies are rarely definitive, however, and must be supplemented by focused microbiological and pathological evaluations of affected sites, considering likely pathogens. Two clinically important parameters in evaluating cystic and cavitary lesions are the tempo of the disease process and the clinical context. The diagnostic possibilities are strongly influenced by knowing whether a radiological lesion is acute or subacute vs chronic (>1 month in duration). This distinction is usually based on the duration and course of related symptoms and signs as well as comparison to previous imaging studies, when available. Acute and subacute processes that evolve over a relatively short period (days to a few weeks) generally suggest infectious or other progressive inflammatory disorders as well as disorders of cardiovascular (embolic) or traumatic causes. Chronic processes are more likely due to neoplastic diseases, long-standing inflammatory or fibrotic disorders, and congenital lesions. The clinical context is crucial and includes age, sex, smoking history, immunocompetency, underlying diseases, drug or other treatments, associated extrapulmonary symptoms and signs, environmental and occupational exposure, recent trauma, travel history, and relevant laboratory test results.

The clinical importance of cystic and cavitary lung diseases is related to their underlying nature. Active infectious processes and malignancies obviously need to be diagnosed promptly to minimize adverse outcomes. Other causes of cystic and cavitary lung disease with potentially devastating outcomes include pulmonary embolism and vasculitides such as Wegener granulomatosis. In addition, the presence of cysts and cavities in the lung predisposes to the occurrence of spontaneous pneumothorax.

Diagnostic approach for lung cavitiess is presented in the table.

Cystic lung disease can occur in a number pathological conditions. A lung cyst is an air filled structure with perceptible wall typically 1mm in thickness but can be up to 4mm. The diameter of a lung cyst is usually less than 1cm. By definition lung cyst can be distinguished from cavity where the wall is greater than 4 mm. However, in practice clear separation of the two entity can sometimes be difficult. The lesion can be focal, multifocal or diffuse. Cystic and cavitary lung lesions can be caused by a diverse array of pathologic processes. In evaluating a patient with such lung lesions, it is helpful to distinguish cysts

from cavities and to categorize focal or multifocal vs diffuse distribution. These characteristics correlated with the tempo of the disease process and the clinical context provide the basis for prioritizing the diagnostic possibilities that will guide the subsequent evaluation.

Table 10.3 — Differential diagnosis for lung cavities

Signs	Tuberculosis	Lung abscess and necrotizing pneumonia	Bullous emphysema
Risk factors	Alcoholism and social risk factors	Aspiration	Usually not found
Symptoms	Chronic respiratory symptoms and intoxication Undulate progressing Habitus phthisicus	Subacute onset Severe intoxication Coughing with plentiful sputum, often bloody (in abscess hack coughing first then withlavish foul smelling purulent sputum after getting drainage to bronchi	Often asymptomatic Often first manifests with spontaneous pneumothorax
Chest X-ray and CT	Upper lobe rigid caverns with fibrosis Commonly accompanied with dissemination and infiltrates.	Generally round in shape Cavity containing an air-fluid level Similar in both frontal and lateral projections	Thing walled ringformed shadows predominantly in apex and subpleural areas Large air spaces (bullae) surrounded by relatively normal lung tissue.
Laboratory tests	MBT + sputum	Sputum investigation: Staphylococcus aureus Klebsiella pneumonia Pseudomonas aerogenosa Proteus sp	Normal
Biopsy	Not indicated due to sputum positivity	Not indicated	Bullous lesion
Diagnostic approach	Reiterated sputum investigation for MBT	Estimating respond to antibiotic, clinical and X-ray dynamic within 3–4 weeks	Thoracoscopy with localized surgical biopsy

Congenital lung malformations are rare and vary widely in their clinical presentation and severity, depending mostly on the degree of lung involvement and their location in the thoracic cavity. They can manifest at any age and can be the source of significant morbidity and mortality in infants and children. Individuals with congenital lung malformations can present with respiratory symptoms at birth or can remain asymptomatic for long periods.

High-resolution CT of the chest is a valuable procedure in characterizing cystic and cavitary diseases. Morphology, location, distribution, and associated radiological findings provide important clues to the nature of the underlying disease.

11. PREVENTION IN THE COMMUNITY. BIOSAFETY AND HOSPITAL CONTROL

By far the best way to prevent tuberculosis is to diagnose and isolate infectious cases rapidly and administer appropriate treatment until patients are rendered noninfectious and the disease is cured. Additional strategies include BCG vaccination and treatment of persons with latent tuberculosis infection who are at high risk of developing active disease.

11.1. Social risk factors of active TB disease developing. Improving access to care for high-risk groups.

Social risk factors have a great role in active TB disease developing. Social prophylaxis includes social-economic measures on the national level which are directed to improvement of vital rate of the population, to protect environment, development of physical training and sport, sanatoriums network and recreation center. The social prophylaxis is aimed at improving the environmental and labor conditions, increasing the population's material well-being, strengthening people's health through the development of mass physical culture andpropaganda of healthy life style, improvement of nourishment and home living conditions, as well as fighting alcoholism and other harmful habits. The effective prevention in community bases on early detection of TB cases and isolation of contagious patients.

Improving access to care for high-risk groups

Patients with tuberculosis often belong to the most disadvantaged population groups that have the most difficulty in accessing health care. Every effort must be made to improve the accessibility of care for these population groups, by providing free tuberculosis treatment; and decentralizing health services to make them more accessible for marginalized groups (in the poorest urban areas), in centers for drug-dependent individuals or alcoholics, in prisons, and in psychiatric services.

The most threaten groups are:

- ✓ material poor-being and poor nourishment;
- ✓ migrants;
- ✓ refugees;
- ✓ prisoners;
- ✓ homeless;
- ✓ crowded and unfavorable living conditions;
- ✓ alcohol addicted.

In high TB prevalence countries crowded living conditions and poor family income increase the risk of infection and active TB disease.

All TB control activities are financed by national budget including the treatment of hospitalized patients and providing treatment on an outpatient basis.

Legislation on communicable disease control is an essential expression of national political commitment. Legislation should respect human dignity and rights as well as public health. However, legislation should make provision for certain extraordinary situations where involuntary compliance with key measures is required to protect public health, subject to appropriate safeguards (e. g. mandatory medical examinations, isolation,quarantine).

11.2. Bacille de Calmette et Guérin vaccine. Organization of BCG-vaccination in high and low TB prevalence countries. Individual contraindications and complications of the BCG vaccination. Treatment of latent tuberculous infection (preventive chemotherapy).

BCG is the most widely used vaccine in the world. In the light of the results of various studies on BCG and the analysis of the different vaccination policies worldwide, WHO made the following recommendations:

- BCG vaccination should be included in national vaccination programs
- In countries with a high prevalence of tuberculosis, BCG vaccination should be administered to infants as soon as possible after birth, and in any case before the age of 1 year.
- In areas where tuberculin testing is used to decide whether individuals should be revaccinated, this practice should be stopped.
- In individuals who are BCG-vaccinated, revaccination is not recommended, and there is no scientific justification for this practice. Multiple revaccination is never recommended.

As BCG is a live vaccine whose mechanism depends on cellular immunity, the risks related to vaccination and its benefits in terms of protection of the child should be taken into account in determining the vaccination strategy.

BCG was derived from an attenuated strain of M. bovis and first administered to humans in 1921. Many BCG vaccines are available worldwide; all are derived from the original strain, but the vaccines vary in efficacy, ranging from 80% to nil in randomized, placebo-controlled trials. A similar range of efficacy was found in recent observational studies (case-control, historic cohort, and cross-sectional) in areas where infants are vaccinated at birth. These studies also found higher rates of efficacy in the protection of infants and young children from relatively serious forms of tuberculosis, such as tuberculous meningitis and miliary tuberculosis.

BCG vaccine is safe and rarely causes serious complications. The local tissue response begins 2–3 weeks after vaccination, with scar formation and healing within 3 months. Side effects—most commonly, ulceration at the vaccination site and regional lymphadenitis—occur in 1–10 % of vaccinated persons. Some vaccine strains have caused osteomyelitis in ~1 case per million doses administered. Disseminated BCG infection and death have occurred in 1–10 cases per 10 million doses administered, although this problem is restricted almost exclusively to persons with impaired immunity, such as children with severe combined immunodeficiency

syndrome or adults with HIV infection. BCG vaccination induces TST reactivity, which tends to wane with time. The presence or size of TST reactions after vaccination does not predict the degree of protection afforded.

BCG vaccine should not be used in children who are known to be HIV-positivebecause of the increased risk, reported from some settings, of severe and often fataldisseminated BCG disease.

In infants whose HIV status is unknown and who are born to HIV-positive mothers and who lack symptoms suggestive of HIV, BCG vaccine should be given after considering local factors.

Latent Tuberculosis Infection: Treatment

Latent tuberculosis infection (LTBI) is defined as a state of persistent immune response to stimulation by *Mycobacterium tuberculosis* antigens without evidence of clinically manifested active TB. One-third of the world's population is estimated to be infected with M. tuberculosis. The vast majority of infected persons have no signs or symptoms of TB disease and are not infectious, but they are at risk for developing active TB disease and becoming infectious. The lifetime risk of reactivation TB for a person with documented LTBI is estimated to be 5–10 %, with the majority developing TB disease within the first five years after initial infection. However, the risk of developing TB disease following infection depends on several factors, the most important one being the immunological status of the host.

Reactivation TB can be averted by preventive treatment.

Identification of at-risk populations for LTBI testing and treatment

- Systematic testing and treatment of LTBI should be performed in people living with HIV, adult and child contacts of pulmonary TB cases, patients initiating anti-tumour necrosis factor treatment, patients receiving dialysis, patients preparing for organ or haematologic transplantation and patients with silicosis. Either interferon-gamma release assays (IGRA) or Mantoux tuberculin skin test (TST) should be used to test for LTBI.
- Systematic testing and treatment of LTBI should be considered for prisoners, health workers, immigrants from high TB burden countries, homeless persons and illicit drug users. Either IGRA or TST should be used to test for LTBI.
- Systematic testing for LTBI is not recommended in people with diabetes, people with harmful alcohol use, tobacco smokers.

Individuals should be asked about symptoms of TB before being tested for LTBI. Chest radiography can be done if efforts are intended also for active TB case finding. Individuals with TB symptoms or any radiological abnormality should be investigated further for active TB and other conditions. TST or IGRA can be used to test for LTBI.

Treatment options for LTBI

The following treatment options are recommended for the treatment of LTBI: 6-month isoniazid, or 9-month isoniazid, or 3-month regimen of weekly rifampicin plus isoniazid, or 3–4 months isoniazid plus rifampicin, or 3–4 months rifampicin alone.

11.3. Respiratory isolation of persons with active TB disease as a measure to limit MBT transmission. Screening and management of active TB contacts. Tuberculosis in cattle — boving TB control.

Tuberculosis in the lung is by far the most important source. Coughing and talking produce very small droplets that contain TB. They are so small that they float in the air. These may be inhaled and cause infection and then disease. The closer someone is to the patient and the longer the two live together, the higher the chance that the person in contact with the patient will inhale TB. An infant of an infectious mother will be at particular risk.

Chemotherapy rapidly reduces infectiousness, usually within 2 weeks, if the bacilli are susceptible. This is why good treatment of all tuberculosis patients, and particularly patients with a direct positive sputum smear, is by far the most effective method of prevention. But if treatment is not continued for the full period, the patient may develop disease again and become infectious again.

In prevention, the most important priority is to diagnose patients with a direct positive sputum smear and to make sure that they complete a standardized treatment. These sputum-smear-positive patients are also usually the most ill. They need treatment urgently to save their lives.

Contact investigation

Those who live in the same household as a person with pulmonary tuberculosis should be examined for evidence of tuberculous infection and disease. All individuals with respiratory or extrapulmonary symptoms indicative of tuberculosis should undergo diagnostic examination and, if shown to have tuberculosis, given treatment.

The implementation of TB contact investigation activities by the NTP should use clear definitions of the TB index case and contacts, procedures to be used in evaluating contacts, policies for treating LTBI and monitoring of the results of contact investigations.

Decisions about contact investigation and treatment of LTBI should be based on the burden of TB in the country and the resources available.

Table 11–1 — Definitions for contact investigation

Index case	●all smear-positive pulmonary TB cases ●all children with TB ●smear-negative pulmonary TB cases ●any form of pulmonary TB irrespective of its bacteriological status
Contacts	●any household member at the moment of the identification of the index case ●all children in the household, especially those aged under 5 years ●individuals in congregate settings (e.g. the workplace, schools, social gatherings, prisons, hospitals, other health facilities) if prolonged contact with an index case has taken place.

The index case should be interviewed as soon as possible after diagnosis to identify contacts. The interview should, as a first priority, focus on the household, but the questions should cover other environments, as mentioned above.

A home visit should be made to obtain a clearer understanding of the patient's circumstances and to confirm the results of the interview.

All identified prioritized contacts of the index case should be instructed to come to the health facility for evaluation. The identified contacts should be listed; if they do not appear for evaluation, a home (or other setting) visit should be made. As a priority, every effort should be made to assess children and people living with HIV/AIDS or those with other conditions and situations associated with an increased risk of TB. After listing the contacts, the results of their assessment should be recorded.

The procedure for screening TB contacts should be clearly defined. The evaluation may be limited to determining whether the contact has symptoms that may suggest TB. As a minimum, all adolescent and adult TB contacts should be asked whether they have a persisting cough (> 2 weeks). Sputum smear examinations should be carried out on those with a persistent cough. All children and HIV should be more thoroughly assessed for TB, including of extrapulmonary sites.

Four important considerations should be taken into account when providing treatment:

1) Any contact identified as having active TB should be registered and treated.

2) Children aged under 5 years who are close contacts and who do not have evidence of TB should be systematically treated with isoniazid chemoprophylaxis: 5 mg/kg daily for six months.

3) Children aged 5 years and above who are in good health do not require chemoprophylaxis but should be followed up on a clinical basis.

4) HIV who are close contacts of an infectious index case and who do not have evidence of TB should be treated with isoniazid: 300 mg/day for 6–9 months.

All patients receiving isoniazid preventive therapy should be seen at regular intervals at least early in the course of treatment to determine whether any adverse effects of isoniazid occur and to encourage adherence. After completing treatment, patients should be asked to seek care if a cough or other possible symptoms of TB develop; there is no need for further follow-up. Contacts with no evidence of TB should be asked to visit a health facility if a persistent cough or other symptoms develop in the following weeks or months.

11.4. Tuberculosis infection control activities — aims and levels.Biosafety and hospital control. The high TB transmission risk zones.

Health-care workers are at much higher risk of TB infection and disease compared with the general population. In health-care settings, other non-medical staff may also be at risk through contact with infectious sources. Measures to control infection are needed in all settings where there is a significant risk of

transmission of TB infection. These settings include general health facilities where patients with cough and in whom pulmonary TB has been diagnosed are in close contact with health staff and others in a crowded and poorly ventilated environment. Waiting rooms (or corridors) where patients and accompanying people, including children, wait to receive medical care are often areas of particular risk.

In hospitals, the risk of transmission is relatively high, especially in pulmonary disease wards. The risk of spread increases when the prevalence of HIV in the contacts (staff and other patients) is high. Laboratories, particularly those carrying out *M. tuberculosis* culture procedures, are also high-risk areas. Other high-risk settings include institutions such as jails, prisons and detention centers, and drug rehabilitation centers. Other situations, such as enclosed environments during prolonged travel, may require special attention.

The main infection control measure is the proper organization and implementation of case detection procedures. Patients receiving adequate treatment are rapidly rendered non-infectious.

Infection control strategies.

The three levels of TB infection control are:

• **workplace and administrative** control measures reduce the exposure of staff and patients;

• **environmental** control measures reduce the concentration of infectious droplet nuclei;

• **personal** protective equipment (respiratory protection) protects staff in specific settings where the concentration of droplet nuclei cannot be adequately reduced by administrative and environmental control measures.

Each level operates at a different point in the transmission process.

Workplace and administrative control measures

Workplace and administrative control measures have the greatest impact on preventing TB transmission. They serve as the first line of defense for preventing the spread of TB in health-care settings. The goals are to prevent TB exposure of staff and patients and to reduce the spread of infection by ensuring rapid and recommended diagnostic investigation and treatment for patients and staff suspected or known to have TB.

The five components of good workplace and administrative control are:

• an infection control plan;

• administrative support for procedures contained in the plan, including quality assurance;

• training of health-care and other staff;

• education of patients and increasing community awareness;

• coordination and communication with the TB control program.

Each facility should have a written TB infection control plan with a protocol for the prompt recognition, separation, provision of services, investigation for TB and referral of patients with suspected or confirmed TB disease. A designated infection control officer is responsible for overseeing the

implementation of infection control measures and providing infection control training for healthcare and other staff who may be exposed to TB infection.

All staff working in a facility should understand the importance of infection control policies and their role in implementing them. As part of training, each health-care worker and staff member, including any lay workers, should receive job category-specific instruction. Training should be conducted before initial assignment, and continuing education should be provided to all employees and volunteers annually.

Reminders that health-care workers and other staff can develop TB, regardless of previous infection status or BCG vaccination, should be given as part of annual retraining on infection control. Staff should be investigated for TB free of charge if they have a cough for two weeks or longer. The infection control plan should list designated staff members to be contacted to initiate confidential TB investigations.

Patients should receive instruction on how to protect others from exposure to TB by simple cough hygiene measures.

Environmental control measures

Environmental controls are the second line of defense for preventing the spread of TB in health-care settings. It is important to recognize that if workplace or administrative controls are inadequate, environmental controls will not eliminate the risk. Many environmental control measures are technically complex and expensive, and therefore only practical for referral hospitals.

Environmental controls include:

• ventilation (natural and mechanical);

• filtration;

• ultraviolet germicidal irradiation.

Ventilation. Controlled natural ventilation considerably reduces the risk of spreading *M. tuberculosis*. When fresh air enters a room, it dilutes the concentration of particles in room air, such as droplet nuclei containing *M. tuberculosis*. Natural ventilation relies on open doors and windows to bring in air from the outside; controlled natural ventilation includes checks to ensure that doors and windows are maintained in an open position that enhances ventilation. Fans may also assist in distributing the air. However, the use of ceiling fans isonly justified if there is free air flow out from the room through open windows. Designing waiting areas and examination rooms to maximize natural ventilation can significantly reduce the spread of TB. In warm climates, open-air shelters with a roof to protect patients from sun and rain are appropriate.

Negative pressure ventilation is another method used to prevent contaminated air from flowing out of the room into adjacent areas in laboratory or health-care facilities, by maintaining an air pressure difference between the two areas. Air is drawn into the room from adjacent areas and exhausted directly to the outside, removing and diluting any infectious particles. This may be the

method of choice in some settings, depending on factors including climatic conditions and available resources. The necessary equipment requires continued maintenance and the air exchange rate may be less than that achieved by well-designed natural ventilation.

When patients provide sputum smear specimens for TB diagnosis, they should do so outside, in the open air away from other people. When this is not possible because of climatic constraints, it should be done in an adequately ventilated booth and not in small rooms such as toilets or other enclosed areas.

***Filtration*.** In small rooms with a limited number of patients or in other small, enclosed areas, room air cleaners with high efficiency particulate air (HEPA) filters may be a useful alternative to mechanical ventilation requiring structural changes. Room air cleaners with HEPA filters may be free-standing or may be permanently attached to floors or ceilings to minimize tampering. Correct maintenance of the filter is essential.

Ultraviolet germicidal irradiation.*M. tuberculosis* is killed if the organisms are exposed to sufficient ultraviolet germicidal irradiation. However, effectiveness depends on close contact with the UV light source and may be limited if humidity is high (over 60 %) and where dust levels are high. UV lights should be directed to the ceiling, associated with adequate air flow and regularly maintained.

Personal protective equipment (respiratory protection)

Personal respiratory protection involves training in the selection and use of respirators. Respirators should not be relied upon to protect health care workers from inhaling *M. tuberculosis* in the absence of standard workplace and environmental controls. Theiruse should be restricted to specific high-risk areas in hospitals and referral centers, such as rooms where spirometry or bronchoscopy are performed or specialized treatment centers for patients with MDR — TB.

Respirators should be distinguished from face masks, such as surgical masks made of cloth or paper. Use of face masks is not generally recommended for health-care staff because they do not protect against TB transmission by aerosol.

However, the use of face masks in high-risk settings for drug resistant-TB is recommended for patients to reduce the risk of droplet nuclei generation and spread, particularly in high-prevalence HIV settings where many health-care workers may be HIV-infected. Respiratory protection may be used as an interim measure while selected administrative and/or environmental control measures are awaiting implementation.

Areas that potentially present a higher risk of transmission:

- respiratory isolation rooms;
- ambulatory and phthisiology waiting rooms;
- thoracic radiology room;
- bronchoscopy and sputum induction rooms;
- pentamidine nebulization room;
- ventilatory assistance areas;

- day-hospital;
- emergency rooms;
- autopsy room;
- microbiology/mycobacteria laboratory.

11.5. Tuberculosis laboratory biosafety

Laboratory biosafety is the process of applying a combination of administrative controls, containment principles, practices and procedures, safety equipment, emergency preparedness, and facilities to enable laboratory staff to work safely with potentially infectious microorganisms; biosafety also aims at preventing unintentional exposure to pathogens or their accidental release.

The main risks in a TB laboratory are related to the aerosols generated during the procedures that could be inhaled by laboratory workers. The risk of aerosolization is associated with the:

- Type of procedure.
- Frequency of testing, and the laboratory's workload.
- Consistency of the material and its predisposition to aerosolize (for example, viscous liquids versus dry solids).
- Bacillary load of the materials.

TB laboratory facilities can be classified into three main levels of procedural risk, based on the activities being performed and their associated risks:

• low TB risk;
• moderate TB risk;
• high TB risk (such as a TB-containment laboratory).

The probability of aerosols being generated is a key factor to consider in determining the level of risk and the necessary mitigation or control measures.

Table 11.2 — Risk precaution levels, associated laboratory activities and risk assessment for TB laboratories

Risk level of TB laboratory	Laboratory activities	Assessment of risk
Low risk	Direct sputum-smear microscopy; preparation of specimens for use in an automated nucleic acid amplification test cartridge.	Low risk of generating infectious aerosols from specimens; low concentration of infectious particles
Moderate risk	Processing and concentration of specimens for inoculation on primary culture media; direct DST (for example, line-probe assays on processed sputum)	Moderate risk of generating infectious aerosols from specimens; low concentration of infectious particles
High risk(TB-containment laboratory)	Culture manipulation for identification; DST or line-probe assays on cultured isolates	High risk of generating infectious aerosols from specimens; high concentration of infectious particles

The international biohazard warning symbol and sign must be displayed on the laboratory door.

Protective laboratory clothing must be worn at all times while staff are working in the laboratory.

The use of engineering controls (for example, biological safety cabinets and room ventilation) and personal respiratory protection (such as respirators) can help prevent laboratory-acquired tuberculosis (TB) infections associated with the inhalation of infectious aerosols. However, the most important consideration in reducing the risk of infection in the laboratory is to minimize the production of aerosols.

12. PRINCIPLES OF TUBERCULOSIS CONTROL.

12.1. Tuberculosis as a global problem. WHO promoted TB control measures — DOTS and Stop TB strategies.

Principles of Tuberculosis Control

The highest priority in any tuberculosis control program is the prompt detection of cases and the provision of short-course chemotherapy to all tuberculosis patients under proper case-management conditions, including directly observed therapy. In addition, in low-prevalence countries with adequate resources, screening of high-risk groups (such as immigrants from high-prevalence countries, migratory workers, prisoners, the homeless, substance abusers, and HIV-seropositive persons) is recommended. TST-positive high-risk persons should be treated for latent infection. Contact investigation is an important component of efficient tuberculosis control, a great deal of attention has been given to the transmission of tuberculosis (particularly in association with HIV infection) in institutional settings such as hospitals, homeless shelters, and prisons. Measures to limit such transmission include respiratory isolation of persons with suspected tuberculosis until they are proven to be noninfectious (i.e., by sputum AFB smear negativity), proper ventilation in rooms of patients with infectious tuberculosis, use of ultraviolet irradiation in areas of increased risk of tuberculosis transmission, and periodic screening of personnel who may come into contact with known or unsuspected cases of tuberculosis. In the past, radiographic surveys, especially those conducted with portable equipment and miniature films, were advocated for case finding. Today, however, the prevalence of tuberculosis in industrialized countries is sufficiently low that «mass miniature radiography» is not cost-effective.

DOTS strategy

In high-prevalence countries, many tuberculosis control programs have made good progress in reducing morbidity and mortality during the past decade by adopting and implementing the DOTS strategy promoted by the WHO. DOTS means — Directly Observed Treatment, Short-course. This strategy consists of:

1. political commitment with increased and sustained financing;

2. case detection through quality-assured bacteriology (starting with microscopic examination of sputum from patients with cough of >2–3 weeks' duration);

3. administration of standardized treatment, with supervision and patient support;

4. an effective drug supply and management system;

5. a monitoring and evaluation system, with impact measurement (including assessment of treatment outcomes — e. g., cure, completion of treatment without bacteriologic proof of cure, death, treatment failure, and default—in all cases registered and notified).

In 2006, the WHO indicated that, while DOTS remains the essential component of any control strategy, additional steps must be undertaken to reach the 2015 tuberculosis control targets set within the United Nations Millennium Development Goals.

Thus, a new **«Stop TB Strategy»** with six components has been promoted:

1. Pursue high-quality DOTS expansion and enhancement.
2. Address HIV-associated tuberculosis, MDR tuberculosis, and other special challenges.
3. Contribute to health system strengthening.
4. Engage all care providers.
5. Empower people with tuberculosis and communities.
6. Enable and promote research.

As part of the fourth component, new evidence-based International Standards for Tuberculosis Care, focused on diagnosis, treatment, and public health responsibilities, have recently been introduced for wide adoption by medical and professional societies, academic institutions, and all practitioners worldwide.

12.2. Evaluation of National Tuberculosis Program. Basic, intermediate and national level of management. NTP in Belarus.

EVALUATION OF A NATIONAL TUBERCULOSIS PROGRAM

Each National Tuberculosis Program should establish objectives for its activities, keeping in mind the ultimate goals of reducing deaths, disease and infection. Evaluation of the program’s activities provides an indication of how well these objectives have been achieved. The evaluation is based on the records kept in each district; evaluation is always made by «cohort analysis» which signifies that all patients recorded in a register within a specified calendar quarter are accounted for within the analysis (no patients are «conveniently» left out).

National Tuberculosis Program in Belarus.

In Belarus National Tuberculosis Program is based on WHO Program and includes all the pointes of DOTS and Stop-TB Strategy.

In modern epidemiological and economic conditions the prompt identification of infectious forms of tuberculosis is the first of all priority. At the same time the wide application of radiological methods of diagnostics allows to carry out early detecting of smear-negative cases that is optimum for the patient's individual prognosis.

Thus the main methods of TB case finding are:

— radiography;

— microbiological diagnostics (bacterioscopy and culture method of sputum or other clinical specimens (lymph node aspirate, cerebrospinal fluid, etc.) examination);

— tuberculin skin test in children and teenagers

Besides, the radiography still remains to be the one of the most actual methods of the active and early diagnostics of chest tumors, heart diseases and other chest abnormalities in adults that makes its wide application even more reasonable.

Today in Belarus the radiological examination of adults is annually performed in the high TB prevalence regions, whereas in the rest areas (the most part of Belarus) the annual radiography is used in persons with social and medical risk factors (migrants, the homeless, prisoners, HIV infection, diabetes, an immunosupression, malignant diseases, etc.), and also in the groups of individuals that have by their professional activities the high risk of MBT transmission to a large number of people (employees of medical and child care facilities, the food industry). Other people are examined once per two years.

Microbiological diagnostics is the integral component of screening. Bacterioskopy is performed according to the WHO standards and added with the culture methodthat provides the gold standard for the definitive diagnosis of TB and allows to test drug sensitivity of MBT for the optimal individual treatment tactics if needed. Culture method also allows to carry out the monitoring of primary and secondary drug resistance of MBT in Belarus.

Tuberkulin skin test is an approximate method of diagnostics used in children and teenagers. It allows to reveal the contingent with the high risk of tuberculosis. The value of tuberkulin skin test increases by annually performance followed with analysis of an eventual individual tuberculin sensitivity.

12.3. Epidemiological indices (tuberculosis morbidity and mortality rate, disease incidence and prevalence, drug resistant TB and HIV-TB surveillance).

The extent of tuberculosis and its evolution over time defines its epidemiology. Epidemiology provides the basis for public health practice needed to control the disease. Various epidemiological indices are employed that differ in complexity.

Mortality — the number of deaths caused by the disease has traditionally defined the extent of the tuberculosis epidemic. Mortality is expressed as the number of tuberculosis deaths per unit of population (usually 100000) and per unit of time (usually per year). However, this information is not reliably collected in most countries where tuberculosis is common.

Tuberculosis is the cause of an estimated 2,8 % of deaths in the world in all age groups — and 26 % of avoidable deaths in developing countries.

Practical point: tuberculosis kills more young people and adults than any other infectious disease; someone dies of tuberculosis every 10 seconds.

Morbidity — tuberculosis morbidity is expressed by two main indices: prevalence and incidence.

Disease prevalence is the number of cases of disease present in thecommunity at any given point in time per unit of population (usually 100000).

Prevalence can be determined only by surveys conducted on representative samples of the general population. These surveys are costly and difficult, but have been conducted in certain countries to monitor the epidemiological trend of tuberculosis.

Disease incidence is expressed by the number of cases of a disease newly occurring over a specific period of time (usually one year) per unit of population (usually 100000).

An estimation of incidence is obtained from notifications of new cases. The estimation is in exact because not all cases that occur during the year are diagnosed, and those that are diagnosed are not always notified. The incidence of tuberculosis cannot be accurately estimated by notification of cases; in general estimations of incidence based on notified cases is lower than the real incidence, as only 30–60 % of cases are notified in many countries. The notified cases are usually specified by type (i.e. pulmonary tuberculosis, smear-positive or smear-negative, extrapulmonary). The incidence of tuberculosis can also be predicted from estimates of the incidence of tuberculous infection. This is reliable only in regions that do not have a high incidence of HIV.

Table 12.1 — Epidemiological variables and parameters of tuberculosis

Variables or indicators:	
Mortality rate	the number of deaths due to tuberculosis per 100000 population per year
Morbidity rate Prevalence Annual incidence	 the number of cases at a given moment per 100000 population the number of new cases in one year per 100000 population
Infection Prevalence Annual incidence	 the percentage of the population infected at a given moment the percentage of the population newly infected in one year

- a smear-positive case remains infectious for an average of 2 years (in the absence of treatment, during the natural course of the disease, the prevalence is estimated to be twice the incidence)
- in one year, 25 % of untreated cases die — this is the case-fatality rate: the annual number of deaths is four times lower than the prevalence and two times lower than the incidence

All of these parameters are affected by the application of National Tuberculosis Programs, and especially chemotherapy.

Gender distribution

While females often predominate among tuberculosis cases in those under 20 years of age, there is a predominance of males among all notified tuberculosis cases and among those dying from tuberculosis in most countries. Among women, tuberculosis kills more women than any cause of maternal mortality.

Table 12.1 — Epidemiological variables and parameters of tuberculosis in Belarus (2013)

Variables or indicators	Definition
Mortality rate	5,7 per 100000 population per year
Morbidity rate Prevalence Annual incidence	 per 100000 population 47,8 per 100000 population (new cases — 38,3)
MDR	34,6 % of new cases 70,8 % of

12.4. The impact of the HIV epidemic.

Tuberculosis is one of the most common diseases among HIV-infected persons worldwide. In some African countries, the rate of HIV infection among tuberculosis patients reaches 70–80% in certain urban settings. A person with a positive TST who acquires HIV infection has a 3–13 % annual risk of developing active tuberculosis. A new tuberculosis infection acquired by an HIV-infected individual may evolve to active disease in a matter of weeks rather than months or years. TB develops in HIV-infected hosts at a yearly rate of 8 % by either of the two pathogenic mechanisms: endogenous reactivation or exogenous reinfection.

Thus the principle points of the HIV epidemic impact are following:

1. All of the parameters are affected by the HIV epidemic

2. The risk of developing tuberculosis is 10 times higher in an HIV-positive individual than in a seronegative individual living in the same conditions

3. The case-fatality rate is higher for HIV-positive tuberculosis patients than for HIV-negative patients

Impact on morbidity

Individuals with HIV and tuberculosis co-infection have a much greater risk of developing active tuberculosis disease than the general population. In countries with high tuberculosis prevalence, tuberculosis is an early manifestation of HIV infection and presents in the majority of cases as smear-positive pulmonary tuberculosis. Extra pulmonary tuberculosis, particularly tuberculosis pleurisy, lymphadenitis and pericardial tuberculosis, is more common in HIV-positive individuals. The annual risk of developing active tuberculosis disease for co-infected patients is on average 10 % (between 5 and 15 %). In countries with high numbers of co-infected patients, there has been an increase in the overall number of tuberculosis cases because HIV infection occurs in the age groups in which the majority of individuals already have tuberculous infection.

In countries with low tuberculosis prevalence, tuberculosis is not the principal opportunistic infection observed, as HIV infection occurs in population groups that have not previously been infected by the tubercle bacillus.

Impact on mortality

Tuberculosis that occurs in AIDS- and HIV-positive patients can be cured using the treatment regimens prescribed for all tuberculosis patients. However, the proportion of patients who die while on treatment is higher, but this is often due to conditions unrelated to tuberculosis.

13. ORGANIZATION OF CASE-FINDING.

13.1. The passive case-finding of patients presenting with symptoms suggestive of tuberculosis (suspects). Smear-positive individuals identifying. Collection of sputum samples.

The organization of tuberculosis case-finding should enable the sources of infection in the community (i.e. those with pulmonary tuberculosis) to be identified. The most effective method is passive case-finding, which consists of identifying pulmonary tuberculosis patients from among those who present to the health services of their own accord. **The main objective of case-finding is to identify smear-positive pulmonary tuberculosis patients, who are the most potent sources of infection.** These patients are found among adults (individuals aged over 15 years), as tuberculosis in children is rarely smear-positive and smear-negative patients rarely transmit disease, even if they are positive on culture.

The system used to evaluate patients presenting with symptoms suggestive of tuberculosis (suspects) is often likened to a *funnel* with a series of filters that identify smear-positive cases among symptomatic individuals:

The top of the *funnel* represents all adult patients presenting to the health care services. This number depends on the accessibility of the health services and the degree of confidence in the health system.

- The first filter is the clinical examination: among patients presenting with general symptoms, the staff working at the primary level of the health services must identify those with respiratory symptoms. On average 10–15 % of adults presenting to the general health services have respiratory symptoms.
- The second filter is also a clinical examination: this distinguishes patients who have symptoms of less than 3 weeks' duration, who most probably have acute respiratory infection. Among those with longer duration of symptoms are not only tuberculosis patients but also patients with chronic lung disease. Of all patients presenting to the health services with respiratory symptoms, 10–25 % have a long-term or chronic condition. Tuberculosis patients most frequently have symptoms of at least 3 weeks (distinguishing them from those with acute respiratory infection) but usually of less than one year (distinguishing them from those with asthma or other chronic lung conditions). These patients are termed «tuberculosis suspects».
- The third, bacteriological, filter is indispensable, as it is the only means by which the most potent sources of infection can be identified. At least three smear microscopy examinations are performed to detect tuberculosis in all those individuals designated «tuberculosis suspects» after passing through the previous filters.

Collection of sputum samples

A PTB suspect should submit three sputum samples for microscopy.The chances of finding TB bacilli are greater with three samples than with two samples or one sample. Secretions build up in the airways overnight. So an early morning sputum sample is more likely to contain TB bacilli than one taken later in the day.

It may be difficult for an outpatient to provide three early morning sputum samples. Therefore in practice an out-patient usually provides sputum samples as follows:

day 1	sample 1	Patient provides an «on-the-spot» sample under supervision when presenting to the health facility. Give the patient a sputum container to take home for an early morning sample the following morning.
day 2	sample 2	Patient brings an early morning sample.
	sample 3	Patient provides another «on-the-spot» sample under supervision

How to organize the collection of sputum samples

When tuberculosis suspects are identified, bacteriological examination of their sputum is necessary. These examinations are performed in the multipurpose laboratory of the basic management unit where there are trained and quality controlled microscopists. The microscopists are responsible each year for diagnosing the 100 to 200 infectious tuberculosis cases in the area served. They are also responsible for the regular bacteriological follow-up of patients during treatment. The sputum specimens must reach the laboratory in good condition. For each tuberculosis suspect, ***three*** sputum specimens should be collected. *One* specimen is collected on the spot on the day of the consultation, the *second* is produced at the patient's home the next day on waking (a sputum container with a tightly fitting lid is provided for this purpose), and the *third* specimen is collected at the laboratory on the same day. As the quality of the sputum specimen is important, the patient should be shown how to produce an adequate sample on coughing. Great care must be taken during this demonstration and when the patient is producing the actual specimens to ensure that there is adequate ventilation to prevent dangerous exposure to a potentially infectious patient. For this reason, it is often wise to undertake this procedure out of doors in the fresh air. If the tuberculosis suspect lives near the center, or can travel to it easily, the specimens are collected in the presence of the laboratory technician. If the patient is detected at a center that is a long way from the laboratory and transport of the samples to the laboratory is organized once or twice a week, applying the recommended procedures of conservation and transport, sputum collection can be done at the community health center. If there is no organization of transport of sputum samples, all tuberculosis suspects should be referred to the laboratory at the basic unit of management.

13.2. The role of radiography and tuberculin skin test in case-finding.

Chest radiography is not widely used in high prevalence countries, as X-ray facilities are frequently not available in the primary health services and the skills required to correctly interpret them are not present at that level. Furthermore, chest radiography is not necessary for detecting smear-positive patients; it is useful mainly for diagnosing pulmonary tuberculosis in patients whose smear examinations are negative. However, chest X-ray provides early case finding which is most important for individual healing prognosis. Thus routine X-ray, if

available, is the most effective method of finding smear-negative active TB cases. TST is not value in adults due to impossibility to identify active TB disease but it remains to be effective in children as provides possibility to identify the moment of getting first infected and high risk groups.

13.3. Tuberculosis register. Categories of TB patients for registration on diagnosis.

Tuberculosis register is kept in each basic management unit

By keeping the tuberculosis register up to date, the main case-finding indicators can be determined for each unit, each year:

1. *The total of all newly notified cases, corresponding to all patients recorded in the register at the time of commencing treatment.*

2. *Classification of smear-positive pulmonary tuberculosis cases by their status at the time of notification:*

- new cases;
- relapses;
- failures;
- return to treatment after default.

When the program is poorly run there will be a high rate of previously treated patients, as the patients are not cured. As the NTP becomes better organized, the proportion of re-treatment cases will fall and most patients will be new cases.

3. *Classification of new pulmonary tuberculosis cases by bacteriological status:*

- smear-positive pulmonary tuberculosis,
- smear-negative pulmonary tuberculosis.

4. *Site of disease:*

- pulmonary tuberculosis;
- extrapulmonary tuberculosis.

Depending on the country, extrapulmonary tuberculosis represents 15–35 % of all tuberculosis cases. This figure varies depending not only on the situation, but also on the technical ability to diagnose extrapulmonary tuberculosis.

5. *The age and sex distribution of smear-positive pulmonary tuberculosis cases* provides an indication of the age groups mainly affected by the disease and its evolution over time.

6. *The notification rate of new smear-positive tuberculosis cases per 100000 population (based on annual estimates of population size).*

The indicators used for new cases can also be used for newly notified relapses. All of the information necessary for performing these evaluations is noted in the Tuberculosis Case Notification Register if it is properly kept up to date. This why it is so important to keep the register correctly and to train the health staff to update it.

Quarterly case-finding reports are prepared by each basic management unit and kept at a **national level**. This centralization allows case-finding to be reviewed at intermediate and national levels for each of the basic management units. The rate of notified smear-positive pulmonary tuberculosis can thus be determined at national and intermediate levels as well as at the level of the basic management unit.

14. ORGANIZATION OF TREATMENT

14.1. Organization of directly observed treatment course in urban and rural areas. The problem of patient non-adherence.

ORGANIZATION OF TREATMENT

The basic management unit, generally located in the main urban center of the district, is responsible for organizing the treatment of all of the tuberculosis patients in the area. Organization of patient treatment requires the application of adapted organizational measures so as to ensure that treatment is directly observed at least during the initial phase and that patients comply with their treatment until cure.

Tuberculosis can be cured only if the drugs are taken regularly. The choice of the place of treatment depends on two factors: the **state of the patient**, and the ability of the health staff to **provide treatment to patients**.

During the initial phase of treatment

During the initial phase of treatment, which always contains rifampicin, the patient must take the drugs in front of the health worker who is responsible for verifying that the patient **swallows all of the prescribed drugs every day**.

- If the patient lives, or can be housed, near a basic management unit, he or she can attend every morning to take the drugs.
- If the patient lives near a health post with staff who are trained and acknowledged to be capable by the district coordinator, treatment can be entrusted to this health post, but the follow-up of the patient must continue to be done by the basic management unit and systematic and regular visits must be made to the health post by the unit coordinator.
- If directly observed treatment can not be provided on an out-patient basis, or if the state of the patient requires it, the patient should be hospitalized during the whole of the initial phase of treatment.

Nevertheless, the application of outpatient-based directly observed treatment is not always easy:

- **In urban areas,** especially in big cities, there are often too few health care insitutions, or they are poorly distributed and are not always able to provide correct patient management. These difficulties are further enhanced in some countries by the HIV epidemic and the rapid increase in the numbers of patients needing to be cared for by each center.
- **In rural areas** the distances that patients need to travel in order to reach a basic management unit are sometimes too long or difficult (remote areas, bad weather, lack of transport or transport too costly for the patient).

Patients for whom directly observed treatment cannot be provided on an outpatient basis must be hospitalized throughout the initial phase of treatment. Hospitalization is a costly way of providing treatment, and alternative local solutions have already been identified in many countries: short-term renting of a room in the city, or accommodation in a shelter created for this purpose.

Supervised treatment refers to helping patients to take their TB medications regularly and to complete TB treatment. It is also meant to ensure that the providers give proper care and are able to detect treatment interruption. One example of treatment supervision is recording each dose of anti-TB drugs on the patient's treatment card. A treatment supporter observing intake of every dose ensures that a TB patient takes the right anti-TB drugs, in the right doses, at the right intervals. Regular supervision and support help to maintain frequent communication between the patient and a health worker or treatment observer; this provides more opportunities for TB education, identification and resolution of obstacles to treatment, and early identification of non-adherence – allowing interventions to return the patient to the prescribed treatment. Regular supervision also allows the prompt detection and management of adverse drug reactions and clinical worsening of TB.

Supervised treatment should be carried out in a context-specific and patient-friendly manner.

14.2. Monitoring of TB patients during treatment - sputum conversion, clinical and chest X-ray monitoring.

It is important to monitor all TB patients, adults and children, during treatment.

Bacteriological monitoring is readily available only for patients with sputum smear-positive PTB. These are usually adults and sometimes older children.

Monitoring of patients with sputum smear-positive PTB:

- **At the end of the initial phase** sputum conversion is observed in most cases. If the patient is still smear-positive the initial phase should be prolonged by 1 month.
- **At the end of the 4th month** for 6-month regimens, and at the end of the 5^{th} month for 8-month regimens.
- **During the last month** (at the 6th or 8th month, depending on the regimen).

Routine monitoring of treatment response by CXR is unnecessary and wasteful of resources.

Clinical monitoring is the usual guide to treatment response for other TB patients. These include adults with sputum smear-negative PTB and extrapulmonary TB and most children.

14.3. The prompt detection and management of adverse drug reactions and clinical worsening.

The identification of side-effects is first of all clinical. Patients should be informed about any possible side-effects and encouraged to report any symptoms that seem unusual during treatment. They should be warned that their urine may take on a reddish or orange colour caused by the rifampicin and that this has no biological significance.

Anti-tuberculosis drugs are generally well tolerated. There are a number of minor side-effects that do not necessitate interruption of treatment but that should be identified and managed so that patients do not stop treatment of their own accord.

Major side-effects are rare, but treatment must be stopped as soon as they occur, either because they can be fatal or because they may lead to functional impairment.

Table 14.1 — Symptom-based approach to management of drug side-effects

Side-effects	Drug(s) probably responsible	Management
Minor		**Continue anti-TB drugs**
anorexia, nausea, abdominal pain	rifampicin	give tablets last thing at night
joint pains	pyrazinamide	give aspirin or nonsteroidal anti-inflammatory drug
burning sensation in feet	isoniazid	give pyridoxine 50–75 mg daily
orange/red urine	rifampicin	Reassurance
Major		**Stop drug(s) responsible**
skin itching/rash	streptomycin	stop anti-TB drugs
deafness (no wax on auroscopy)	streptomycin	stop streptomycin, give ethambutol instead
dizziness (vertigoand nystagmus)	streptomycin	stop streptomycin, give ethambutol instead
jaundice (other causes excluded)	most anti-TB drugs	stop all anti-TB drugs until jaundice resolves
vomiting and confusion (suspected drug-induced pre-icteric hepatitis)	most anti-TB drugs	stop anti-TB drugs, urgent liver function tests
visual impairment	ethambutol	stop ethambutol
generalized, including shock and purpura	rifampicin	stop rifampicin

14.4. Treatment outcome recording and «cohort analysis» of treatment results.

Recording treatment outcome

At the end of the treatment course in each individual patient, the district TB officer should record the treatment outcome as follows:

Cure	patient who is sputum smear-negative in the last month of treatment and on at least one previous occasion
Treatment completed	patient who has completed treatment but does not meet the criteria to be classified as a cure or a failure
Treatment failure	patient who is sputum smear-positive at 5 months or later during treatment
Died	patient who dies for any reason during the course of treatment
Defaulted (treatmentinterrupted)	patient whose treatment was interrupted for2 consecutive months or more
Transferred out	patient who has been transferred to another recording and reporting unit and for whom the treatment outcome is not known

How to evaluate the results of treatment

At the level of the basic management unit The treatment outcome of diagnosed patients is evaluated by **cohort analysis**. This analysis is based on the information recorded in the tuberculosis register. Certain indicators enable the progress of the NTP towards the global objective of a cure rate of 85% to be measured. They also highlight any weaknesses in the organisation of treatment, which can then be remedied. We will illustrate this analysis using the example of new smear-positive cases of pulmonary tuberculosis.

An early indication of treatment efficiency is provided by the rate of smear conversion: this is the proportion of smear-positive cases with negative smears at the end of the second month of short-course chemotherapy (or at the end of the third month in the case of re-treatment cases) out of all smear-positive cases registered for treatment.

Quarterly reports are completed separately for the various types of case (new smear-positive and re-treatment smear-positive cases; new smear-negative and extra-pulmonary cases are not usually evaluated). The treatment outcome of the cohort enables the following rates to be determined for a specified quarter. All outcomes can be determined for smear-positive cases; cure and failure cannot be considered outcomes where new smear-negative cases are evaluated.

Cured	This is the proportion of smear-positive cases who have completed treatment and who have at least two negative sputum smear tests (one of these during the last month of treatment), out of all new smear-positive cases registered for treatment.
Completed treatment	This is the proportion of cases who have completed treatment, but for whom cure is not confirmed by two bacteriological examinations, out of the total number of cases registered for treatment. *If this rate is high, the health center should do its best to provide proof of cure by bacteriologically testing patients who have completed treatment, most of whom are likely to have been cured.* The success rate is obtained by adding together the cure rate and the completed treatment rate.
Failure	This is the proportion of smear-positive cases who remain or revert to being smear-positive 5 months or later after commencing the course of treatment, out of the total number of smear-positive cases registered for treatment. *In a well-functioning NTP the failure rate should be lower than 5 %.*
Defaulted	This is the proportion of cases who have interrupted their treatment for 2 or more months, out of the total number of new smear-positive cases registered for treatment.

	This rate clearly reflects the quality of the organization of a tuberculosis control center, and should be less than 10 % in an efficient NTP. When this rate is too high (more than 15 %), the causes should be analysed and corrective measures should be taken.
Transferred out	This is the proportion of cases who have been transferred to another district (or to another province) during the course of treatment, out of the total number of cases registered for treatment, and whose results of treatment are unknown. *Where results are obtained from the center where the patient continued treatment, these results should be entered for the patient instead of «transferred out».*

Indicators of treatment outcome are useful to guide implementation and identify problems to be solved. Targets should be action-oriented, thus emphasis should be placed particularly on the proportion of cases who have defaulted or been transferred out.

The cohort analyses are sent to the intermediate and national levels, thus allowing the NTP to be analysed by basic management unit, intermediate level and for the whole country, for surveillance purposes and to improve the program. This analysis should aid, for example, in making the decision to improve patient management: closer supervision of certain basic units, creation of new treatment centers, and retraining of health staff. Cohort analysis performed on a regular basis allows the progress of the NTP to be measured over time.

Other ways of analysing the success of an NTP

- **Quality control of microscopists** is organized at national or intermediate level, and permits ongoing evaluation of each district's microscopists. It also identifies those laboratory technicians who need retraining or training and those who need to be replaced. It usually consists of re-reading of a sample of sputum slides prepared for routine diagnosis.
- **Drug resistance surveillance** gives a clear indication of the quality of treatment: when a program is first set up the rates of acquired and primary resistance may be high, due to the lack of organized treatment in the past. If standardized regimens are consistently applied and patient treatment is organized correctly, these rates will gradually decrease over time, thus providing proof of the effectiveness of the program.
- **Surveillance of HIV seroprevalence** — HIV surveillance should be performed in order to better plan, manage and evaluate the NTP. This provides a clearer analysis of the program's results, as it can explain, for example, a sudden increase in case numbers and/or an excess death rate recorded for tuberculosis cases. It can also help NTP managers to anticipate problems that may arise in organizing the management of a greater number of patients, and to find solutions.

The ongoing evaluation of program activities depends principally on the regular upkeep of the tuberculosis register. The regular updating of the registers and the quality of the quarterly reports are checked during the regular supervisory visits organized by the central and/or intermediate level. Review of the reports at the national level allows the NTP to be evaluated in its entirety, thus enabling the central unit to manage and make improvements to the NTP.

An evaluation is conducted each year by the WHO based on the data provided by the NTP of each country.

CONCLUSION

Tuberculosis must be one of the principal preoccupations of public health, as it potentially affects the entire community, appears at every level of the health service and has major economic implications. This is why it is essential for all those involved in tuberculosis control to be capable of assuming responsibility in both medical and social domains.

The medical students of today are the physicians of tomorrow. They will play a central role in leading the health teams who will operate National Tuberculosis Programs in the years to come.

The future of these programs depends on their professional competence.

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Буйневич Ирина Викторовна
Гопоняко Светлана Владимировна

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