

**MINISTRY OF HEALTH CARE OF UKRAINE  
KHARKIV NATIONAL MEDICAL UNIVERSITY**

Department of Phthisiology and Pulmonology  
Faculty II medical

**METHODICAL RECOMMENDATION  
FOR THE STUDENT'S SELF WORK  
DURING THE PREPARATION FOR PRACTIICAL CLASS**

Educative discipline Internal medicine with infectious diseases and phthisiology  
For students of 6 Course of Medical faculty

**“Approved”**

Educative-Methodical counsel of  
Department  
of Phthisiology and Pulmonology  
“ ” 20\_\_ p.  
Protocol № \_\_\_\_\_  
Head of Department

Professor Shevchenko O.S

“ ” 2014

Kharkiv – 2014

**Topic.** Case tuberculosis management:

Individual approach for patient treatment. Patient adherence to TB treatment. Monitoring the patient by health care workers: treatment of the patient on inpatient and on ambulatory regime. Standards of TB patients treatment. Practical approach to Lung health (PAL). Standardisation of Clinical aid. Coordination within health care service. Differential diagnosis of dissemination, infiltrative changes, nodular and round shadows, cavitory formations in the lungs.

Additional laboratory and instrumental methods of examination (rapid cultural methods of MBT revealing: BACTEC, Xpert MTB/RIF, molecular based laboratory methods: Nucleic Acid Amplification (NAA) Tests, Tuberculosis serological tests, high-resolution CT of thorax cage, fiber-optic bronchoscopy with bronchial lavage sampling for microscopy and cultural investigation, Transcatheter bronchial lung biopsy/trans-thoracic needle biopsy or open punctional biopsy of lungs, thoracoscopy with biopsy of pleura (pleurocentesis) with exudate sampling for microscopy and cultural investigation).

Secondary prophylaxis of tuberculosis.

**1. Quantity of hours** \_\_\_6\_\_\_\_\_

**2. Methodical support of the topic:** tables, results of surveys of patients and their case histories, X-ray pictures.

**3. Actuality of the topic**

The diagnosis of TB refers to the recognition by health workers (medical officer, nurse, paramedic or other) of an active case, i.e. a patient with current disease due to *M. tuberculosis*.

Care of patients with tuberculosis (TB) starts with a quality assured diagnosis. Successful expansion of directly observed treatment (short course) (DOTS) and programmatic management of drug-resistant and HIV-associated TB therefore require a robust network of TB laboratories with adequate biosafety, modern methods of diagnosis, standard operating procedures and appropriate quality assurance.

That is why a student has to master of the main methods of TB treatment knowledge and the skills to use it in medical practice.

**4. - General goal:** to master of the knowledge and the skills of the main methods to TB diagnose, rendering medical aid, treatment supervision, directly observed therapy, patient-centred care, measures to prevent interruptions of treatment and to use it in medical practice.

**- The concrete aims:**

**a)** To know the duration of chemotherapy course and multiplicity of administration of anti-TB drugs for every of chemotherapy regimens;

To master of the main principle of TB patient treatment, the combinations of anti-TB drugs;

To know standardized chemotherapy regimens depending on treatment category;

To know the criteria of TB patient recovery;

To know the epidemiological, clinical, radiological and other criteria evident for regression and recovery of TB;

To know signs of side-effects of anti-TB drugs;

To know the modern methods of detection of *M.tuberculosis* in pathological material and rapid detection of their sensitivity to the anti-TB drugs of I-st and II-nd line.

To have a clear understanding about residual changes which are almost always accompany the recovery of tuberculosis and their significance for possible reactivation (exacerbation or relapse of TB in the future).

**b)** To be able to differentiate of pathological shadows on expectation X-ray (disseminative, nodular, round, infiltrative, cavitory formations in the lungs, intrathoracic lymph nodes pathology);

To be able to prescribe the methods of prevention of possible adverse reactions, induced by anti-TB drugs and complications which can be appear during the treatment

To be able to eliminate side effects of anti-TB drugs in case of their appearance;

To be able to assessing the patient's adherence to the regimen;

To be able to choose a necessary additional laboratory or instrumental methods of examination.

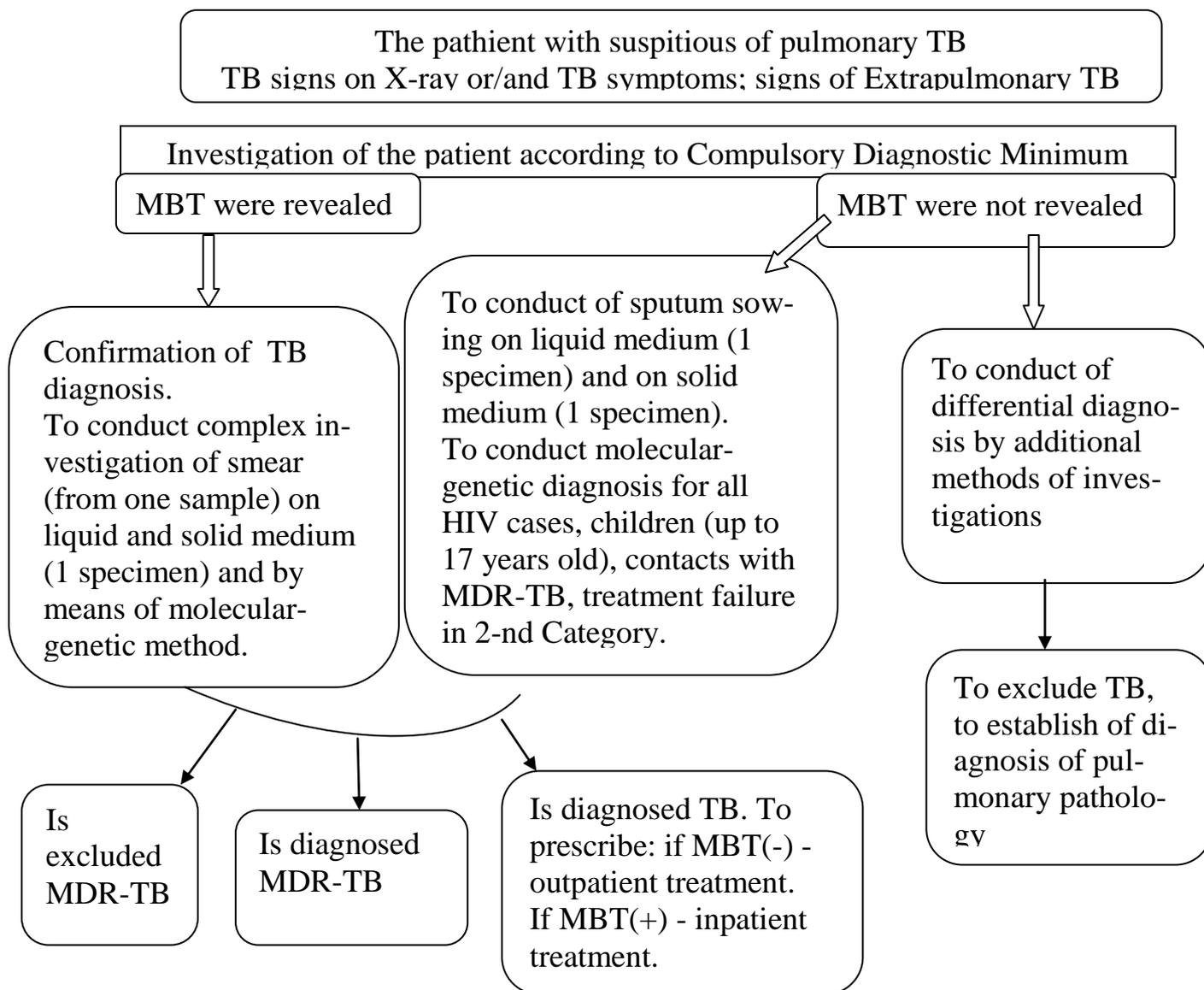
**c) Practical skills**

- To perform individual approach for TB diagnose and treatment;
- To assess the result of compulsory and additional methods of investigation
- To perform adequate secondary prophylaxis of TB
- To perform monitoring the patient on inpatient and on ambulatory regime.
- To carry out assessing the results of molecular based laboratory methods, rapid cultural methods of MBT revealing.
- To evaluate the results of additional noninvasive and invasive diagnostic procedures.

**5. Graphological structure of the theme.**

The detection of TB cases requires that affected individuals are aware of their symptoms, have access to health facilities and are evaluated by health workers (doctors, nurses, medical assistants, clinical officers) who recognize the symptoms of TB. Health workers must have access to a reliable laboratory and ensure that the necessary specimens are collected for examination (see scheme №1). This is a complex set of activities and behaviours, and failure at any stage can cause delays in diagnosis or misdiagnoses.

**Scheme №1. ALGORITHM OF DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS IN INPATIENT INSTITUTIONS**



### Standard regimens for defined patient groups

Standardized treatment means that all patients in a defined group receive the same treatment regimen. For assigning standard regimens, patients are grouped by the same patient registration groups used for recording and reporting, which differentiate new patients from those who have had prior treatment. Registration groups for previously treated patients are based on the outcome of their prior treatment course: failure, relapse and default (interrupted).

<b>Standardized case definitions</b>	(section 7.1) The list of the main terms, etc.	(number 11-16).
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### Standard regimens (category) for treatment

<b>Category I</b>
Newly diagnosed TB (NTB) of different localization with MBT (+); Severe forms of NTB different localization with MBT (-): miliary , disseminated TB , destructive pulmonary TB with single cavities more than 3 cm in diameter or if there 's more than 3 smaller cavities ; meningitis, caseous pneumonia , pericarditis , peritonitis , intestinal TB , TB of neural system with complications , urogenital, intrathoracic lymph nodes with involvement of more than 2 groups on the one side, or 2 and more on both sides; complicated TB in children.
<b>Category II</b>
Any cases of previously treated pulmonary or extra-pulmonary TB, which were registered for re-treatment no longer than 12 months: Relaps of TB of different locations with MBT (+); Treatment failure with MBT (+) Treatment after interruption with MBT (+); Other TB with MBT (+) or (-).
<b>Category III</b>
New cases of TB MBT (-) are not referred to Category I. When NTB with MBT(-) has confirmed contact with a confirmed case of MDR-TB (high risk MDR-TB) algorithm is similar to cases of Category I.
<b>Category IV</b>
Patients with MDR-TB and XDR-TB and patients with confirmed cases of drug-resistant TB, which according to the resistance profile is need to be treated more than 12 months.

<b>TB outcomes</b>	(section 7.1) The list of the main terms, parameters and et etc.	(number 26-31).
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### New patients presumed or known to have drug-susceptible TB

New patients are presumed to have drug-susceptible TB with two exceptions:

- Where there is a high prevalence of isoniazid resistance in new patients.
- If they have developed active TB after known contact with a patient documented to have drug-resistant TB; they are likely to have a similar drug resistance pattern to the source case, and DST should be carried out at the start of treatment. While DST results of the patient are awaited, a regimen based on the DST of the presumed source case should be started (**see scheme №2**).

Recommendation also applies to extrapulmonary TB except TB of the central nervous system, bone or joint for which is necessary longer therapy.

Wherever feasible, the optimal dosing frequency for new patients with pulmonary TB is daily throughout the course of therapy (**See table № 1**).

New patients with pulmonary TB may receive a daily intensive phase followed by three times weekly continuation phase [2HRZE/4(HR)<sub>3</sub>] provided that each dose is directly observed.

**Standard regimens for new TB patients (presumed, or known, to have drug-susceptible TB)****Intensive phase treatment**2 months of HRZE<sup>a</sup>**Continuation phase**

4 months of HR

Or 4 months of H<sub>3</sub>R<sub>3</sub>

<sup>a</sup>WHO no longer recommends omission of ethambutol during the intensive phase of treatment for patients with non-cavitary, smear-negative pulmonary TB or extrapulmonary TB who are known to be HIV-negative. In tuberculous meningitis, ethambutol should be replaced by streptomycin.

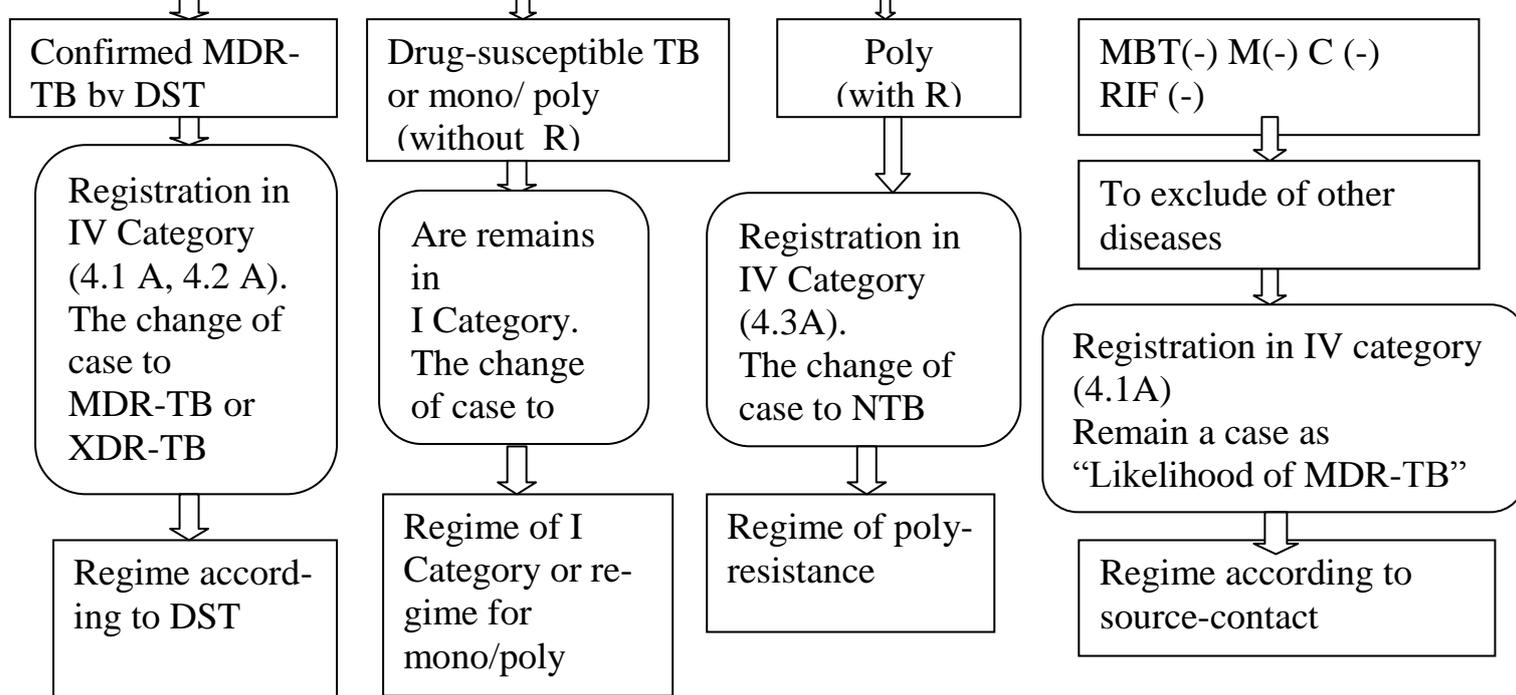
Daily (rather than three times weekly) intensive-phase dosing may help to prevent acquired drug resistance in TB patients starting treatment with isoniazid resistance

H = isoniazid, R = rifampicin, Z = pyrazinamide, E = ethambutol, S = streptomycin

**Scheme № 2. LIKELYHOOD OF MDR-TB ALGORITHM MANAGEMENT**  
**"CONTACT WITH PATIENTS ON CONFIRMED CASE OF MDR-TB"**

Is registered in I category. A case is marks as "likelihood of MDR-TB"

The treatment with empirical use of standard MDR regimens (IV category), according to DST of source till the moment of receiving DST MBT (rapid liquid culture systems or the results of detection of rifampicin resistance, obtained by the Gene Xpert) 1-1,5 month

**Monitoring the patient**

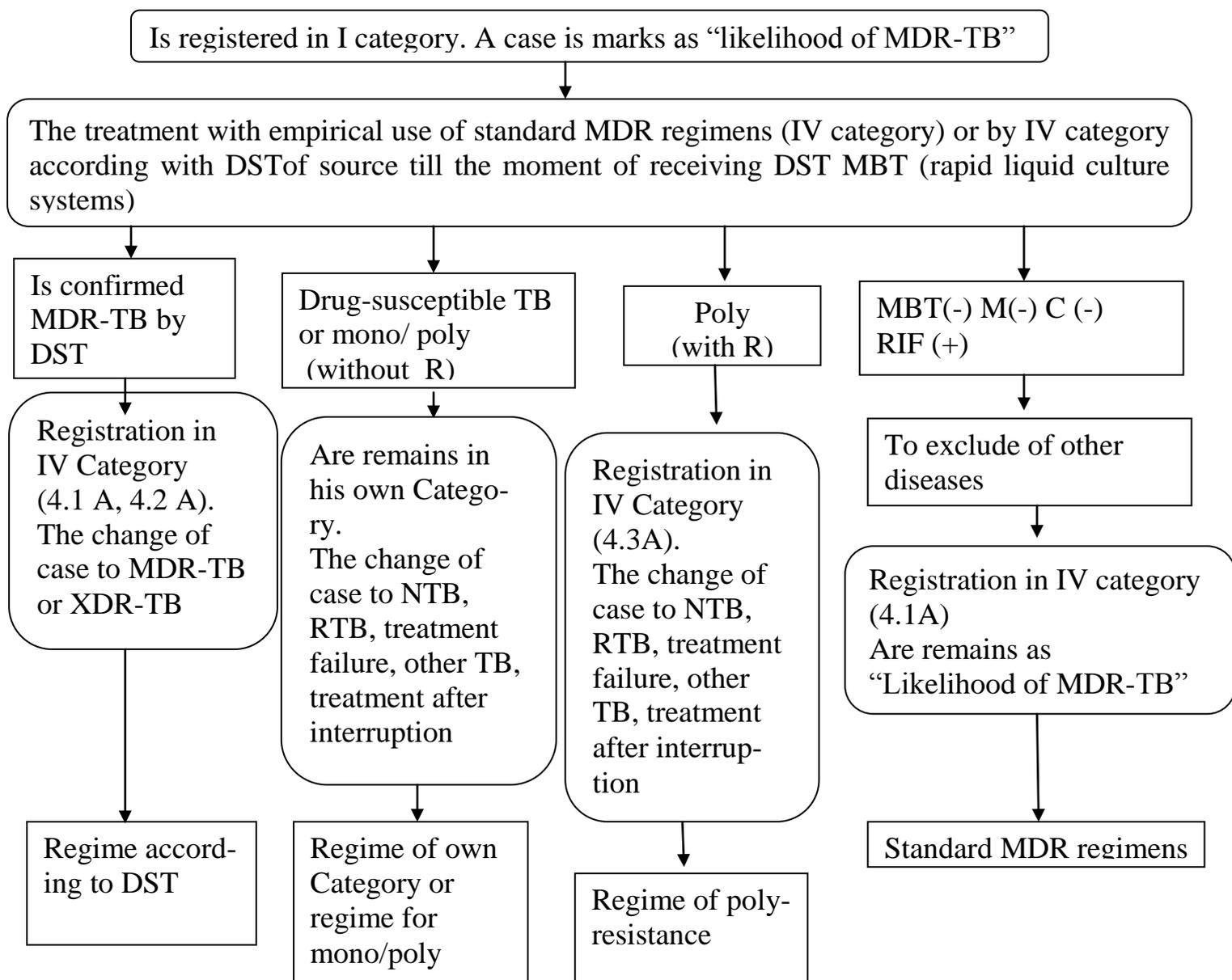
All patients should be monitored to assess their response to therapy. Regular monitoring of patients also facilitates treatment completion and allows the identification and management of adverse drug reactions. All patients, their treatment supporters and health workers should be instructed to report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

A positive sputum smear at the end of the intensive phase may indicate any of the following:

- the initial phase of therapy was poorly supervised and patient adherence was poor;
- poor quality of anti-TB drugs;
- doses of anti-TB drugs are below the recommended range;
- resolution is slow because the patient had extensive cavitation and a heavy initial bacillary load;
- there are co-morbid conditions that interfere either with adherence or with response;
- the patient may have drug-resistant *M. tuberculosis* that is not responding to first-line treatment (see **scheme №3**);
- non-viable bacteria remain visible by microscopy

In new patients, if the specimen obtained at the end of the intensive phase (month 2) is smear-positive, sputum smear microscopy should be obtained at the end of the third month (90 doses of anti-Tb drugs). If smear-positive on 3 month, the result considered as “treatment failure”. Algorithm for their further management – see on **scheme № 4**.

**Scheme №3. LIKELYHOOD OF MDR-TB ALGORITHM MANAGEMENT:  
"PATIENTS WITH RESISTANCE TO RIFAMPICIN RIF(+), WHICH WERE REVEALED  
BY MEANS OF MOLECULAR-GENETIC METHOD"**



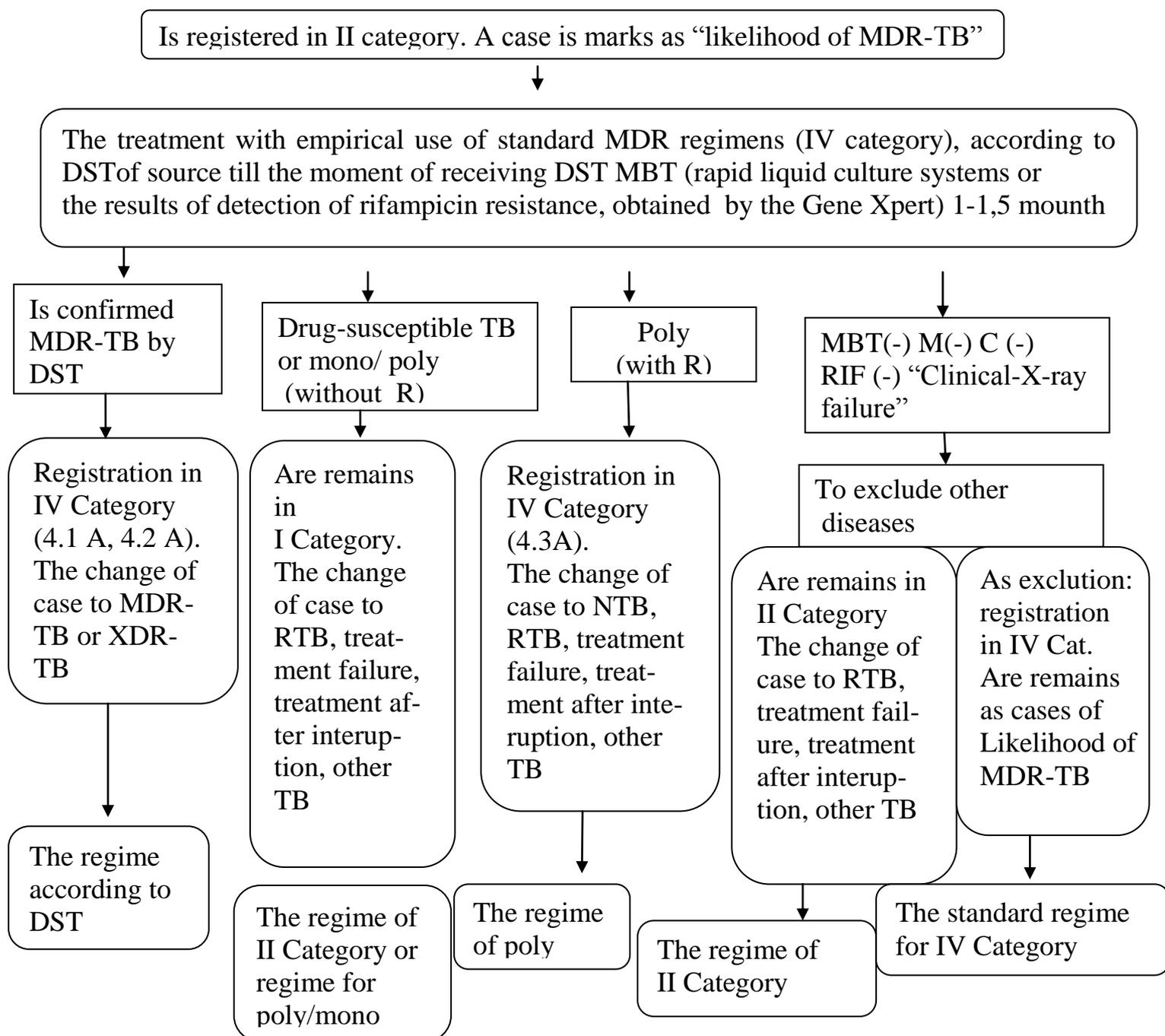
### Previously treated patients

Previous TB treatment is a strong determinant of drug resistance, and previously treated patients comprise a significant proportion (13%) of the global TB.

Of all the forms of drug resistance, it is most critical to detect multidrug resistance (MDR) because it makes regimens with first-line drugs much less effective and resistance can be further amplified. Prompt identification of MDR and initiation of MDR treatment with second-line drugs gives a better chance of cure and prevents the development and spread of further resistance.

Specimens for culture and drug susceptibility testing (DST) should be obtained from all previously treated TB patients at or before the start of treatment. DST should be performed for at least isoniazid and rifampicin. Using conventional DST methods yields results within weeks (for liquid media) or months (for solid media). Because of this delay, countries using conventional methods will need to start an empirical regimen while DST results are awaited. (see scheme №4).

#### Scheme № 4. LIKELYHOOD OF MDR-TB ALGORITHM MANAGEMENT: “TREATMENT FAILURE IN II CATEGORY BY SMEAR/CULTURE



Patients whose prior course of therapy has failed should therefore receive an empirical MDR regimen. Drug resistance surveillance or surveys often show that those relapsing or returning after default have a medium or low likelihood of MDR; such patients can receive the retreatment regimen of first-line drugs. It was designed primarily for use in settings with low prevalence of initial drug resistance and in patients previously treated with a regimen that included rifampicin for the first 2 months.

With line probe assays, MDR can be essentially confirmed or excluded within 1–2 days, which allows the results to guide the regimen at the start of therapy.

Obtaining specimens for conventional culture and DST should not delay the start of therapy in settings where conventional DST results are routinely available for individual patients. Empirical regimens, often based on drug-resistance surveillance data, are used while the results of conventional DST (liquid or solid media) are awaited, and should be started promptly. This is especially important if the patient is seriously ill or the disease is progressing rapidly. Placing a patient on an empiric regimen pending DST is done to avoid clinical deterioration. Also, once empiric therapy begins to render the patient less infectious, the risk of transmission to contacts decreases.

WHO has endorsed the use of liquid culture and rapid species identification as preferable to solid culture-based methods alone. Liquid systems are more sensitive for detecting mycobacteria and may increase the case yield by 10% compared with solid media. Liquid systems may also yield DST results in as little as 10 days, compared with 28–42 days using conventional solid media.

### **Longer delays in receiving DST results mean longer empirical treatment, which has significant disadvantages:**

- With empirical use of the retreatment regimen with first-line drugs, patients whose DST eventually confirms MDR will have been inadequately treated while awaiting DST results. Consequences could include continued spread of MDR and amplification of resistance to include ethambutol.
- With empirical use of MDR regimens, patients whose DST eventually rules out MDR will have been exposed to toxic drugs they did not need while awaiting DST results. Consequences could include adverse drug effects and an increased risk of defaulting from treatment.

In contrast to conventional methods, molecular-amplification assays such as line probe assays allow detection of rifampicin resistance (alone or in combination with isoniazid) within days of sputum specimens being obtained from the patient (and can also be used on cultures obtained from rapid liquid culture systems). Patients with MDR-TB can avoid delays in starting an MDR regimen, and TB patients without MDR will avoid unnecessary second-line drug treatment. WHO strongly encourages the use of rapid molecular (and culture-based) DST in smear-positive persons living with HIV.

### **Management of treatment interruption**

The management of patients who have interrupted treatment takes into consideration several factors, each of which, if present, will necessitate further caution and probably additional treatment :

- The patient is found to be smear- or culture-positive upon returning from default.
- Interruption occurs in the intensive, rather than the continuation, phase.
- Interruption occurs early (rather than later) in the continuation phase.
- The interruption is of long duration.
- The patient is immunocompromised (living with HIV or another condition).
- The patient had poor response to treatment before the interruption.
- Drug-resistant disease is known or suspected.

### **Monitoring and recording adverse effects**

Most TB patients complete their treatment without any significant adverse drug effects. However, a few patients do experience adverse effects. It is therefore important that patients be clinically monitored during treatment so that adverse effects can be detected promptly and managed properly. Routine laboratory monitoring is not necessary.

Health personnel can monitor adverse drug effects by teaching patients how to recognize the symptoms of common effects, urging them to report if they develop such symptoms, and by asking about symptoms when patients come to collect drugs.

#### Symptom-based approach to managing side-effects of anti-TB drugs

A symptom-based approach to the management of the most common adverse effects, which effects are classified as major or minor. In general, a patient who develops minor adverse effects should continue the TB treatment and be given symptomatic treatment. If a patient develops a major side-effect, the treatment or the responsible drug is stopped; the patient should be urgently referred to a clinician or health care facility for further assessment and treatment. Patients with major adverse reactions should be managed in a hospital.

#### Supervised treatment

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.

Directly observed therapy (DOT), a recommended method of supervision, should be seen as a part of a support package that addresses patients' needs. This package should help to ensure that DOT is sensitive to, and supportive of, the patient's needs. 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 also allows the prompt detection and management of adverse drug reactions and clinical worsening of TB.

Direct observation of each dose of drugs is most critical in the intensive phase, when intermittent dosing is used during either phase, and in the treatment of, for example, psychologically handicapped patients, prison inmates, or patients receiving second-line anti-TB drugs. Supervised treatment should be carried out in a context-specific and patient-friendly manner. There must be flexibility in how DOT is applied, with adaptation to different settings that are convenient to the patient. The whole purpose of treatment observation would be defeated if it were to limit access to care, turn patients away from treatment, or add to their hardships.

Depending on the local conditions, supervision may be undertaken at a health facility, in the workplace, in the community or at home. A treatment supporter must be identified for each TB patient; he or she should be a person acceptable to, and chosen with, the patient. For TB patients who live close to a health facility, the treatment supporter will be one of the staff in the health facility, and this is the ideal choice if convenient to the patient. Collaboration with other programmes allows the identification of staff from these programmes who may observe TB treatment.

#### Using a patient-centred approach to care and treatment delivery

For any chosen method of supervision and administration of treatment, a programme must show high sputum smear conversion and cure rates, under routine conditions, in both rural and urban areas.

Accessible, high-quality, continuous **ambulatory TB care** (if treatment is health facility-based)

- expanding treatment outlets in the poorest rural and urban settings and involving providers who practise close to where patients live (thus reducing travel costs and loss of time and wages);
- convenient clinic hours with minimal waiting times;
- adequate numbers of motivated health workers with managerial support;
- flexibility to make appropriate arrangements for transfer to another facility;
- ability to make arrangements upon release from prison or hospital to continue care on an ambulatory basis in the patient's community.

## Availability of hospitalization

Hospitalization is essential for severely ill patients and for those with complications or associated conditions requiring closer clinical monitoring. It might also be an alternative, especially during the initial phase of treatment, for a small number of

patients for whom other means of ensuring treatment adherence and support are not available. However, hospitalization per se does not ensure regular drug intake or completion of the treatment. Patient-centred support and supervision are just as important to success in an inpatient setting as in the community.

**Practical Approach to Lung Health (PAL)** is the patient centred approach to improving quality of diagnosis and treatment of common respiratory illnesses in primary health care settings. It seeks to standardize service delivery through development and implementation of clinical guidelines and managerial support within the district system. It is intended to achieve coordination between the different levels of health care and between TB control and general health services.

### Expected outcomes of the PAL strategy

If properly implemented, the PAL strategy is expected to produce qualitative and quantitative benefits that contribute to strengthening the Primary Health Care system, increasing the effectiveness of the Stop TB Strategy for TB control, and enhancing the competence of health workers at peripheral health units.

### Expected benefits of PAL strategy implementation for tuberculosis case-detection and diagnosis

PAL strategy implementation will help strengthen the coordination between TB control and the PHC system and will improve the process of detecting and diagnosing TB through:

- Identification of TB cases among patients who report a short duration of respiratory symptoms and among severely ill patients.
- Better quality of differential diagnosis in patients with respiratory symptoms and with smear-negative microscopy, particularly in settings of high HIV prevalence and in units with easy access to chest radiography.
- Systematic follow-up of TB suspects until a plausible diagnosis has been made.
- Clear guidelines on systematic TB diagnostic procedures in patients with chronic respiratory symptoms.
- Intensified supervision of TB and PAL case-management activities.
- Increased or sustained visibility of TB among emerging ARIs and CRDs, particularly asthma and COPD.
- Strengthening of the links between the health management information system and the TB information system.

## WHO-recommended techniques

### Microscopy

Sputum specimens should be obtained for microscopic examination from all patients suspected of having pulmonary TB. Conventional Ziehl-Neelsen light microscopy performed directly on sputum specimens is suitable for all levels of laboratory services, including peripheral laboratories at primary health care centres or district hospitals.

Mycobacteria can be distinguished from other microorganisms by their thick, lipid-containing cell walls, which retain biochemical stains despite decolourization by acid-containing reagents (so-called 'acid-fastness').

*Advantages:* Microscopy of sputum smears is simple and inexpensive and allows rapid detection of infectious cases of pulmonary TB. Sputum specimens from patients with pulmonary TB, especially those with cavitory disease, often contain sufficiently large numbers of acid-fast bacilli to be detected by microscopy.

*Disadvantages:* Direct smear microscopy is relatively insensitive, as at least 5000 bacilli per millilitre of sputum are required for a positive result. The sensitivity is further reduced in patients with extrapulmonary TB, those with HIV coinfection and those with disease due to nontuberculous mycobacteria.

*Limitations:* Microscopy for acid-fast bacilli cannot distinguish *M. tuberculosis* from nontuberculous mycobacteria, viable from nonviable organisms or drug-susceptible from drug-resistant strains.

### **Conventional fluorescence microscopy**

As a lower-magnification objective is used to scan smears, a much larger area of the smear can be seen, and therefore less time is needed than with Ziehl Neelsen microscopy. Conventional fluorescence microscopy is on average 10% more sensitive than Ziehl-Neelsen microscopy but requires considerable technical expertise; the capital and running costs are also considerably higher. Conventional fluorescence microscopy is therefore recommended by WHO for use at intermediate laboratory level where more than 100 smears are examined per day.

### **Light-emitting diode (LED) fluorescence microscopy**

Light-emitting diodes (LEDs) provide a much less expensive light source for fluorescence microscopy. LED microscopes or attachments require less power and can run on batteries, and the bulbs have a long half-life and do not release potentially toxic products if broken. In a recent WHO evaluation, the diagnostic accuracy of LED microscopy was found to be comparable to that of conventional fluorescence microscopy and superior to that of conventional Ziehl-Neelsen microscopy. It is therefore recommended that conventional fluorescence microscopy be replaced by LED microscopy and that LED microscopy be phased in as an alternative for conventional Ziehl-Neelsen light microscopy in both high- and low-volume laboratories.

### **Culture and species identification**

*Advantages:* Mycobacterial culture and identification of *M. tuberculosis* provide a definitive diagnosis of TB, significantly increase the number of cases found (often by 30–50%) and allow earlier detection of cases (often before they become infectious). Culture also provides the necessary isolates for conventional DST.

*Disadvantages:* Culture is more complex and expensive than microscopy, requiring facilities for media preparation, specimen processing, growth of organisms, specific laboratory equipment, skilled laboratory technicians and appropriate biosafety conditions.

*Limitations:* Specimens must be decontaminated before culture to prevent overgrowth by other microorganisms. All decontamination methods are to some extent also harmful to mycobacteria, and culture is therefore not 100% sensitive. Good laboratory practice maintains a delicate balance between the yield of mycobacteria and contamination by other microorganisms. Solid and liquid culture methods are suitable for central reference laboratories (or regional laboratories in large countries).

**Solid culture** methods are less expensive than liquid systems, but the results are invariably delayed because of the slow growth of mycobacteria. Several culture methods are recommended.

**Liquid culture** increases the case yield by 10% over solid media, and fully automated, nonradiometric, noninvasive BACTEC MGIT 960 system for detection and drug susceptibility testing of mycobacteria, which reduce the diagnostic delay to days rather than weeks (6-14 days after delivering of pathological material).

MGIT is a commercial liquid culture system from BD and the leading rapid culture method in the developed world. MGIT is manufactured in unbreakable plastic tubes containing enriched culture media. At the bottom of the tube is a silicone plug containing chemicals that become fluorescent when bacteria consume oxygen during the process of growth, making detection possible using either manual or automated systems. MGIT can also be used to perform DST, which is done by comparing the growth of mycobacteria with and without the addition of drugs used to treat TB. The combined use of MGIT for both TB detection and DST can shave months off the conventional process of identifying multidrug-resistant (MDR) TB. Liquid systems are, however, more prone to contamination, and the manipulation of large volumes of infectious material mandates appropriate, adequate biosafety measures.

Despite having been developed over a decade ago, the advantages of MGIT for TB detection were not reaching most endemic settings for several reasons. This was primarily due to the cost of the test, the lack of a simple means to confirm the growth of *M. tuberculosis* species in positive tubes, and the lack of data demonstrating that the use of liquid culture was feasible in resource-constrained settings. MGIT as a solution for case detection and DST in developing countries.

Positive cultures must be identified to differentiate *M. tuberculosis* from nontuberculous mycobacteria, which are more common in HIV-infected patients, with a prevalence that varies from country to country. Diseases due to nontuberculous mycobacteria are treated entirely differently from drug-resistant TB. As a minimum, laboratories performing DST must differentiate *M. tuberculosis* from nontuberculous mycobacteria; further speciation is not recommended. Confirmation is usually done from the biological charac-

teristics of the culture growth and with selected molecular or biochemical tests (which invariably delay the final result).

**Rapid immunochromatographic assays** (so-called strip speciation tests) for species identification on culture isolates provide a definitive identification of *M. tuberculosis* in 15-20 min.

Molecular tests, biochemical methods and strip speciation assays are suitable for laboratories where culture and DST are performed.

### **Drug susceptibility testing (DST)**

*Advantages:* DST provides a definitive diagnosis of drug-resistant TB. A number of techniques are available:

1) **Phenotypic (Culture) methods** involve culturing *M. tuberculosis* in the presence of anti-TB drugs to detect growth (indicating drug resistance) or inhibition of growth (indicating drug susceptibility).

2) **Genotypic methods** target specific molecular mutations associated with resistance against individual drugs.

Phenotypic (culture) DST methods are performed as direct or indirect tests on solid or liquid media.

In *direct testing*, a set of drug-containing and drug-free media are inoculated directly with a concentrated specimen.

*Indirect testing* involves inoculation of drug-containing media with a pure culture grown from the original specimen. Indirect phenotypic tests have been extensively validated and are currently regarded as the gold standard.

*Disadvantages:* DST methods are suitable for use at central reference laboratory level only, given the need for appropriate laboratory infrastructure (particularly biosafety) and the technical complexity of the available techniques and methods.

*Limitations:* The accuracy of DST varies with the drug tested.

### **First-line DST**

DST is most accurate for rifampicin and isoniazid and less reliable and reproducible for streptomycin, ethambutol and pyrazinamide. As a minimum, national TB control programmes for treating MDR-TB patients should establish laboratory capacity to detect MDR. Rifampicin resistance is a valid and reliable indicator or proxy of MDR. Rapid DST is essential for identifying patients at risk for MDR-TB, as a first priority.

**The Line Probe Assay (LPA)** (Product name: **GenoType MTBDRplus®**) – is a DNA strip test that allows simultaneous molecular (nucleic acid amplification) identification of tuberculosis and the most common genetic mutations causing resistance to rifampicin and isoniazid. This technology can diagnose MDR-TB directly from smear-positive sputum samples, providing results in just five hours - an enormous improvement on the 1 to 2 months needed for conventional DST for 1st line drugs.

*Advantages:* Genotypic methods have considerable advantages for scaling-up programmatic management of drug-resistant TB, in particular with regard to speed, standardized testing, potentially high through-put and reduced requirements for biosafety. Molecular LPA allows rapid detection of resistance to rifampicin (alone or in combination with isoniazid).

*Disadvantages:* LPAs do not eliminate the need for conventional culture and DST capability. Currently available LPAs are registered for use only on smear-positive sputum specimens of *M. tuberculosis* isolates grown from smear-negative specimens by conventional culture methods.

*Limitations:* LPAs are suitable for use at central or national reference laboratory level, with potential for decentralization to regional level if the appropriate infrastructure can be ensured.

Automated liquid systems (BACTEC MGIT 960) and molecular GenoType MTBDRplus that is capable of detecting Mycobacterium tuberculosis and carrying out DST for 1st line TB drugs are the current goldstandard. Once MDR-TB has been confirmed, additional first- and second-line drug susceptibility results should be obtained.

### **Second-line DST**

Second-line DST is complex and expensive. Commercial liquid methods and the proportion method on solid medium have been studied; methods for the absolute concentration or resistance ratio on solid medium have not been validated.

Automated liquid systems (BACTEC M GIT 960) for second-line DST are recommended as the current gold standard.

Routine second-line DST is not recommended unless the required laboratory infrastructure and capacity have been established, rigorous quality assurance is in place and sustainable proficiency has been demonstrated. In order to retain proficiency and expertise, it is recommended that second-line DST be performed only if at least 200 specimens from high-risk patients are expected per year.

Aminoglycosides, polypeptides and fluoroquinolones have been shown to have relatively good reliability and reproducibility, allowing a quality-assured diagnosis of XDR-TB.

Routine DST for other second-line drugs (ethionamide, prothionamide, cycloserine, terizidone, paminosalicylic acid, clofazimine, amoxicillin–clavulanate, clarithromycin, linezolid) is not recommended, as the reliability and reproducibility of laboratory testing cannot be guaranteed.

### **Nucleic Acid Amplification (NAA) Tests**

This is a heterogeneous group of tests that use either the polymerase chain reaction (PCR) technique or Transcription mediated amplification (TMA) or other forms of nucleic acid amplification methods to detect mycobacterial nucleic acid. These tests vary in which nucleic acid sequence they detect and vary in their accuracy. The two most common commercially available tests are the amplified mycobacterium tuberculosis direct test (MTD, Gen-Probe) and Amplicor (Roche Diagnostics).

NAA tests directly identify *M. tuberculosis* from sputum specimens by: Amplifying (copying) DNA and RNA segments. Can help guide clinician's decision for patient therapy and isolation. Does not replace need for AFB smear, culture, or clinical judgment. If NAA test and AFB smears are positive: patients are presumed to have TB and should begin treatment. If NAA test is negative and AFB smears are positive: patients may have nontuberculous mycobacteria infection. Smear negative patients: sensitivity 62%, specificity 99%; Smear positive patients: sensitivity 99%, specificity 98%.

#### **Xpert MBT/RIF**

Earlier and improved TB case detection - including smear-negative disease, often associated with HIV co-infection - as well as expanded capacity to diagnose multidrug-resistant tuberculosis (MDR-TB) are global priorities for TB control. Conventional laboratory methods are slow and cumbersome and novel technologies for rapid detection are therefore the focus of TB research and development.

TB-specific automated, cartridge-based nucleic amplification assay (Xpert MTB/RIF) based on the GeneXpert multi-disease platform, currently unique in its simplification of molecular testing with fully integrated and automated sample preparation, amplification and detection required for real-time polymerase chain reaction. Xpert MTB/RIF detects *M. tuberculosis* as well as rifampicin resistance-conferring mutations directly from sputum, in an assay providing results within two hours.

*Cost-effectiveness modeling* indicated that the use of Xpert MTB-RIF significantly increased TB case-finding (by roughly 30%) when used as a replacement or add-on test to microscopy. Use of Xpert MTB/RIF as replacement for conventional culture and DST also significantly increased MDR case-finding (roughly three-fold). The capital and running costs of Xpert MTB/RIF are substantially greater than those of microscopy, though similar to the cost for performing culture and drug susceptibility testing.

- 1) Xpert MTB/RIF should be used *as the initial diagnostic test* in individuals suspected of MDR-TB or HIV-associated TB (strong recommendation);
- 2) Xpert MTB/RIF may be used as a follow-on test to microscopy in settings where MDR and/or HIV is of lesser concern, especially in smear-negative specimens

Xpert MTB/RIF technology does, however, not eliminate the need for conventional microscopy culture and DST, which are required to monitor treatment progress and to detect resistance to drugs other than rifampicin. In settings or patient groups where rifampicin resistance is rare, Xpert MTB/RIF results indicating rifampicin resistance should be confirmed by conventional DST or LPA.

### **Commercial serological tests**

Tuberculosis serological tests almost exclusively rely on antibody recognition of antigens of *M. tuberculosis* by the humoral immune response, as opposed to antigen recognition by the cellular immune response (e.g. interferon-gamma release assays). An accurate serological test that could provide rapid diagnosis of TB and in a suitable format (e.g. point-of-care) would be particularly useful both as a replacement for laboratory-based tests and for extending TB diagnosis to lower levels of health services, especially those without on-site laboratories.

An antibody detection-based diagnostic test in a user-friendly format could potentially replace microscopy and extend tuberculosis diagnosis to lower levels of health services. Commercial serological tests provide inconsistent and imprecise findings resulting in highly variable values for sensitivity and specificity. There is no evidence that existing commercial serological assays improve patient-important outcomes, and high proportions of false-positive and false-negative results adversely impact patient safety. Overall data quality was graded as very low and it is strongly recommended that these tests not be used for the diagnosis of pulmonary and extra-pulmonary TB. However, to date no serological test for TB has proven both specific and sensitive enough to be used as part of routine testing in national disease control programs.

### **CT in tuberculosis**

Chest radiographs play a major role in the screening, diagnosis, and response to treatment of patients with TB. However, the radiographs may be normal or show only mild or nonspecific findings in patients with active disease. Common causes of a missed diagnosis of TB are failure to recognize hilar and mediastinal lymphadenopathy as a manifestation of primary disease in adults, overlooking of mild parenchymal abnormalities in patients with reactivation disease, and failure to recognize that an upper lobe nodule or mass surrounded by small nodular opacities or scarring may represent TB.

CT is more sensitive than chest radiography in the detection and characterization of both subtle localized or disseminated parenchymal disease and mediastinal lymphadenopathy. The radiographic diagnosis of TB is initially correct in only 49% of all cases—34% for the diagnosis of primary TB and 59% for the diagnosis of reactivation TB. With CT, the diagnosis of pulmonary TB is correct in 91% of patients and TB is correctly excluded in 76% of patients. CT and high-resolution CT are particularly helpful in the detection of small foci of cavitation in areas of confluent pneumonia and in areas of dense nodularity and scarring. In one study of 41 patients with active TB, high-resolution CT showed cavities in 58%, whereas chest radiographs showed cavities in only 22%.

In addition to the diagnosis of TB, is useful in determining disease activity. A tentative diagnosis of active TB on CT could be based on the pattern of parenchymal abnormalities and the presence of cavitation or evidence of endobronchial spread, such as the presence of centrilobular nodules or a tree-in-bud pattern.

CT is also helpful in the evaluation of pleural complications, including tuberculous effusion, empyema, and bronchopleural fistula, and may show pleural disease that is not evident on chest radiography.

In addition to its major role in the diagnosis of TB, CT plays an important role in the management of TB, especially in complicated or MDR TB. MDR TB often shows multiple cavities, which lead to the expectoration of a large number of bacilli and endobronchial spread to previously unaffected areas of the lung. Limited drug penetration into the cavities that harbor large numbers of mycobacteria is believed to contribute to the drug resistance. Therefore, surgery may be an adjuvant treatment for MDR TB, although present-day TB treatment relies on chemotherapy. CT can locate the site of cavitation and the extent of active disease and therefore can be a roadmap for the planning of surgical treatment.

The radiographic manifestations of HIV-associated pulmonary TB are thought to be dependent on the level of immunosuppression at the time of overt disease. On CT, HIV-seropositive patients with a CD4 T lymphocyte count  $< 200/\text{mm}^3$  have a higher prevalence of mediastinal or hilar lymphadenopathy, a lower prevalence of cavitation, and often extrapulmonary involvement as compared with HIV-seropositive patients with a CD4 T lymphocyte count equal to or  $\geq 200/\text{mm}^3$ .

### **Tracheobronchoscopy.**

Combination of bronchi and trachea examination. For bronchoscopy are used a rigid(metal) or flexible bronchoscope with fiber glass optics (bronchofiberscope/fiber-optic bronchoscope). At examination of bronchi estimate a condition and ability of bleeding of the mucous membrane, character of bronchi contents, diameter of a bronchi lumen, elasticity, tone and mobility of a bronchial wall. Other deviation from norm are fixed also. An endoscopic picture is photographed. An examination is finished (if it is necessary) by sampling of material pieces for bacteriological and pathologo-anatomical examinations.

### **Bronchopulmonary lavage.**

During bronchoscopy getting of the lavage fluid allows to receive a material for diagnosis verification at negative bacteriological data. Sometimes from the lavage fluid it is possible to reveal MBT, when it is impossible by other ways.

**Trance bronchial lung biopsy.** The direct indication of its realization is the presence of a pathology in main lobe, segmental and subsegmental bronchi. For biopsy various techniques are used: snap off (biopsy forcepsing), erasure by a curette, brush (spongy or brach biopsy), pressing by porolone sponge (sponge biopsy), punction and aspiration.

**Transthoracal needle biopsy.** Is used for getting: - of the pleura and lung tissues for histological investigation; - of biopsy material of the lungs, the pleura and lymphatic nodes by operation – opening of the chest cavity.

**Pleurocentesis (thoracocentesis)** and paracentetic biopsy of the pleura. By method of aspiration (needle) biopsy it is possible to take a material from the pleura and the pleural fluid. From a fluid, received at pleurocentesis, in sterile tubes select probes for laboratory research. Define (determine) the relative density of a fluid, cell composition liquid are defined etc. Pleurocentesis make by a special needle under the control roentgenoscopy. Usually receive two samples of biopsy material, which investigate histologically and on MBT presence.

**Thoracoscopy** is the most accurate yet most expensive tool for establishing the diagnosis of tuberculous pleurisy. In contrast to the newly established video-assisted thoracoscopic surgery, the classic way to perform thoracoscopy is using only local anesthesia and sedation (medical thoracoscopy) making the procedure less invasive and expensive. The leading diagnostic indication for medical thoracoscopy today is an exudative pleural effusion of unknown origin offering a yield of more than 90% in malignancy or tuberculous pleurisy. In addition, talc poudrage during thoracoscopy is the most effective way to perform pleurodesis. For spontaneous pneumothorax, the second most important indication, medical thoracoscopy allows staging as well as therapeutic measures such as coagulation of blebs or talc poudrage. Other indications such as biopsy for diffuse lung disease or peripheral nodules are now reserved for video-assisted thoracoscopic surgery.

### **6. Approximation card for student' work:**

- a) To enumerate of clinical symptoms and results of objective investigations, which are typical for TB;
- b) To make a choice of most informative tests, laboratory and instrumental investigation, which help to detect tentative diagnose. Evaluate of available results of investigations;
- c) Perform the differential diagnosis with two concurrent diseases;
- d) To prescribe the treatment;
- e) To prescribe of pathogenetic treatment;
- f) To prescribe the measures for patient adherence to TB treatment, to prevent interruption of treatment;
- g) To prescribe the measures for secondary prophylaxis of TB relapse;

All listed above tasks student have to answer according to individual practical task. This is takes into consideration before assessing of mastering level of practical classes.

### **7. The tasks for student's self work during the preparation for the class.**

7.1 The list of the main terms, parameters and characteristics which a student has to master during the preparation for the class.

	The term	The definition
1	DOTS – strategy (directly observed treatment short-course)	The program of TB patient treatment carrying out under the direct control after the standardized chemotherapy regimens depending on treatment and dispensary follow up category.
2	Complex treatment	This is combination of specific (etiologic) and non-specific treatment and also using of surgical methods of treatment.
3	Combinative treatment	This is an administration of no less than 4 anti-TB drugs in the initial phase for every patient.
4	Control of treatment	This is a taking of drug at a presence of medical workers, close relatives or voluntaries with a purpose to supply taking drugs regularly.

5	Two phases of treatment	First intensive phase is directed to inhibit the multiplication of Mycobacterium tuberculosis, its significant reducing and part sterilization of a zone of specific inflammation. In second, continuative phase daily or intermittent chemotherapy is provided for clinical recovery of patient (persistent stopping of bacilli excretion, resolving of infiltrates and healing of caverns) or for treatment before surgical intervention.
6	TB suspect	Any person who presents with symptom or signs suggestive of TB. The most common symptom of pulmonary TB is a productive cough for more than 2 weeks, which may be accompanied by other respiratory symptoms (shortness of breath, chest pains, haemoptysis) and/or constitutional symptoms (loss of appetite, weight loss, fever, night sweats, and fatigue)
7	Case of TB	A definite case of TB or one in which a clinician or other medical practitioner has diagnosed TB and has decided to treat the patient with a full course of TB treatment. Any person given treatment for TB should be recorded as a case. Incomplete “trial” TB treatment should not be given as a method for diagnosis.
8	Definite case of TB	A patient with MBT complex identified from a clinical specimen, either by culture or by a newer such as molecular line probe assay. In countries that lack the laboratory capacity to routinely identify M.tuberculosis, a pulmonary case with one or more initial sputum smear examinations positive for acid-fast bacilli (AFB) is also considered to be a “definite” case.
9	Classified cases of TB	Cases of TB, classified according to the: -anatomical site of disease -bacteriological results (including drug resistance) -history of previous treatment -HIV status of the patient
10	Treatment category	This is a group of patients defined on 4 determinants: type of TB (defined on the ground of the disease history), site of TB, severity of the disease and presence of TB bacilli in examined material (sputum).
11	New case of tuberculosis (NTB)	A patient with newly diagnosed tuberculosis at any anatomical site, with smear – positive or smear – negative (culture – the same), who never was treated with anti-TB drugs or was treated less than 1 month.
12	Retreatment case (previously treated cases):	Have received 1 month or more of anti-TB drugs in the past, may have positive or negative bacteriology and may have disease at any anatomical site.
13	Relapse of TB (RTB)	A case of repeated diagnosis of active tuberculosis in patient who in the past successfully completed a full course of chemotherapy and was considered as made a full recovery, or totally completed course of treatment with result “treatment completed”, and bacterioexcretion revealed repeatedly (MBT+) microscopy, culture or molecular-genetic method).
14	Treatment after default (interruption)	A case of repeated treatment after interruption of previous treatment more than 2 month together before completion of course, with MBT(+) or MBT (-)
15	Treatment failure	New case of TB with sputum smear and/or culture is still positive after 90 doses of antiTB drugs have been intaken. OR: due to clinical-X-ray picture progression in case of negative smear and/or culture result. Also included in this definition are patients found to harbour a multi-drug-resistant (MDR) strain at any point of time during the treatment, whether they are smear-negative or -positive.
16	Other case of TB (OTB)	All cases that do not fit the above types of cases, such as patients -For whom it is not known whether they have been previously treated; -Who were previously treated but with unknown outcome of that previous treatment; and/or

		-Who have returned to treatment with smear-negative pulmonary TB (PTB) or bacteriologically negative extrapulmonary TB (EPTB); - Patients with prolonged (chronic) course of TB with multiple episodes of ineffective (interrupted) treatment in the past history with MBT(+)
17	The drugs of first line (essential drugs)	The drugs (isoniazid, rifampicin, pyrazinamide, streptomycin, ethambutol) which are administered to New Case of TB or RTB who excretes drug bacilli (patient of 1- 3 categories).
18	The drugs of second line (reserved drugs)	The drugs (kanamycin, ampicillin, capreomycin, ofloxacin/ciprofloxacin, ethionamide/prothionamide, PAS, cycloserin) which are used in individual schemes of chemotherapy in patients of category 4 with the resistance towards the drugs of first line and also in patients of other categories with the resistance of MBT towards the drugs of first line or with adverse reactions induced by drugs.
19	Intermittent regimen	The taking of daily dose of anti-TB drugs 2-3 times a week.
20	Extensive forms of TB	Tuberculosis involved two and more segments of lungs or 2 and more organs.
21	Intensive phase	The stage of TB patient treatment directed on the inhibition of MBT multiplication, removing acute manifestation of the disease and part sterilization of specific inflammation zone.
22	Continuation phase	The stage of TB patient (daily or intermittent chemotherapy) carrying out to reach clinical recovery of the patient (persistent stopping of bacilli excretion, resolving infiltrates and healing of cavern) or to prepare the patient for surgical intervention).
23	Undeleted adverse reactions	Adverse reactions which could not be to delete after reducing of the drug dosage and administration of adjacent therapy.
24	Deleted adverse reactions	Adverse reactions which characterized by insignificant symptoms and organs function disturbances and could be deleted by reducing of the drug dosage and administration of adjacent therapy.
25	Criteria of TB patient recovery	The batch of signs of good treatment response (completed and adequate main course of chemotherapy; persistent stopping of bacilli excretion, confirmed by microscopy and culture examination of the sputum; healing of caverns in lungs and resolving (or induration) of infiltration and lesions; deleting of clinical and laboratory signs of TB inflammation; restoration of functional abilities and capability of work).
26	Recovery	The patient completed full course of the treatment with recorded negative sputum smear in two or more sequent specimens after 5 months of the treatment and at the end of the treatment.
27	The treatment is completed	The patient with positive sputum smear at the start of treatment completed full course of treatment and no more than one negative result of sputum smear on 5 <sup>th</sup> month and later is recorded. The patient suffering from pulmonary or extra pulmonary tuberculosis with negative sputum smears after full course of the treatment.
28	Treatment failure	New case of TB with sputum smear and/or culture is still positive after 90 doses of antiTB drugs have been intaken. OR: due to clinical-X-ray picture progression in case of negative smear and/or culture result.
29	Default (interrupted)	A patient whose treatment was interrupted for 2 consecutive months or more without any one reason.
30	Died	A patient who dies for any reason during the course of treatment.
31	Transfer out	A patient who has been transferred to another recording and reporting unit and whose treatment outcome is unknown.
32	AFB	Acid fast bacilli
33	MDR-TB	Multidrug- resistant TB

34	XDR-TB	Extensively drug- resistant TB
35	Rapid speciation	Strip speciation for rapid <i>Mycobacterium tuberculosis</i> from nontuberculous mycobacteria; established at regional or central level in combination with liquid culture.
36	DST	drug-susceptibility testing
37	Pulmonary TB (PTB)	Refers to a case of TB (defined above) involving the lung parenchyma. Miliary tuberculosis is classified as pulmonary TB because there are lesions in the lungs. Tuberculous intrathoracic lymphadenopathy (mediastinal and/or hilar) or tuberculous pleural effusion, without radiographic abnormalities in the lungs, constitutes a case of <i>extrapulmonary</i> TB. A patient with both pulmonary and extrapulmonary TB should be classified as a case of <i>pulmonary</i> TB.
38	Extrapulmonary TB (EPTB)	Refers to a case of TB (defined above) involving organs other than the lungs, e.g. pleura, lymph nodes, abdomen, genitourinary tract, skin, joints and bones, meninges. Diagnosis should be based on at least one specimen with confirmed <i>M. tuberculosis</i> or histological or strong clinical evidence consistent with active EPTB, followed by a decision by a clinician to treat with a full course of tuberculosis chemotherapy. The case definition of an EPTB case with several sites affected depends on the site representing the most severe form of disease.
39	Smear –positive	1) A case of pulmonary TB is considered to be <i>smear-positive</i> if one or more sputum smear specimens at the start of treatment are positive for AFB by any one method in case of presence clinical-X-ray signs of active TB process, also if patient has attenuation of active TB or tuberculous changes of indefinite activity. 2) A case of pulmonary TB is considered to be <i>smear-positive</i> if two sputum smear specimens at the start of treatment are positive for AFB even if no X-ray tuberculous changes in lungs. Smear-positive cases are the most infectious and most likely to transmit their disease in their surroundings; they are the focus for infection control measures and contact investigations. Bacteriological monitoring of treatment progress is most feasible and practicable in these patients
40	Sputum conversion	It is 2 consecutive smear-negative and culture-negative samples taken at least 30 days apart.
41	Confirmed monoresistance	It is Tb patient, who excrete MBT with proved in vitro resistance to any one anti-TB drug I line
42	Confirmed polyresistance	It is Tb patient, who excrete MBT with proved in vitro resistance to more than one anti-TB drugs I line, except cases of combined resistance to isoniazid and rifampicin.
43	Confirmed multidrug resistance (MDR)	It is Tb patient, who excrete MBT with proved in vitro resistance minimum to isoniazid and rifampicin.
44	Confirmed extensive drug resistance (XDR)	is a rare type of multidrug-resistant tuberculosis (MDR TB) that is proved in vitro resistance to isoniazid and rifampin, plus any fluoroquinolone and at least one of three injectable second-line drugs (i.e., amikacin, kanamycin, or capreomycin).
45	High likelihood of MDR	1) Known contact with a proven MDR case; 2) “treatment failure” (who remain sputum smear-positive after treatment in 2 category, except for cases of uncontrolled, inadequate course or doses of drugs, low compliance level, treatment inadequacy to mono- or polyresistance); 3) detection of resistance to rifampicin by molecular-genetic investigation. 4) With co-morbid conditions associated with malabsorption or rapid-

		transit diarrhea 5) Exposed in institutions with an MDR outbreak or a high prevalence of MDR (such as certain prisons or mines) 6) have type 2 diabetes mellitus 7) With a history of using anti-TB drugs of poor or unknown quality.
46	Moderate likelihood of MDR	All other cases of repeated treatment, treatment failure or interruption of 1-st course of treatment.
47	Low likelihood of MDR	All other cases of New case of TB

**Practical work (tasks) which have to be done within the class:**

**Materials for the self-control:**

1. What is the typical for molecular-genetic methods of TB diagnosis?
  - A. Allow to detect the DNA of MBT in pathological material
  - B. Results are available during 1-2 days.
  - C. Permit to perform simultaneous molecular identification of tuberculosis and the most common genetic mutations causing resistance to rifampicin and isoniazid.
  - D. It is reasonable to conduct them at the patients with negative results of microscopy of pathological material in case of HIV-infestation.
  - E. All listed above are correct.
  
2. Enumerate of molecular-genetic methods of specific identification of MBT?
  - A. PCR (NAA);
  - B. DNA- strip;
  - C. Biochip;
  - D. GeneXpert
  - E. All listed above
  
3. Implementation of PCR diagnostics of MBT allows:
  - A. To shorten the term of confirmation of TB diagnosis ;
  - B. To shorten the term of revealing of MBT till 1-2 days;
  - C. To control effectiveness of chemotherapy at the patients with negative result of bacterioscopy.
  - D. To directly identify *M. tuberculosis* from sputum specimens and does not replace need for AFB smear, culture, or clinical judgment.
  - E. All listed above
  
4. What kind of methods of identification of MBT allow to distinguish mycobacterium of tuberculous complex from nontuberculous micobacteria?
  - A. PCR (NAA);
  - B. Immunchromatic test (TBc-ID)
  - C. BACTEC MGIT 960
  - D. Culture on Levenstein-Yensen medium;
  - E. Colorimetric method.
  
5. To which kind of person molecular-genetic methods of investigation of pathological material are indicated in the 3-rd month of treatment (90 doses)?
  - A. In case of positive result of microscopy on 3-rd month at the patient with negative result of this method on the onset of the treatment or at the clinical-X-ray negative dynamics.
  - B. In case of negative result of microscopy in the 3-rd month at the patient with negative result of this method on the onset of the treatment or at the clinical-X-ray positive dynamics.
  - C. In case of positive results of microscopy in the 3-rd month at the patient with negative result of this method on the onset of the treatment or in case of absence of clinical-X-ray TB changes.

- D. In case of hyperergic result of microscopy in the 3-rd month at the patient with negative result of this method on the onset of the treatment or at the clinical-X-ray negative dynamics.
- E. In case of positive result of microscopy on 2-rd month at the patient with negative result of this method on the onset of the treatment or at the clinical-X-ray negative dynamics.
6. The technology GeneExpert allows simultaneously:
- To detect belongings of mycobacterium of tuberculous complex during 2 hours;
  - To detect medicamentous resistance during 24 hours;
  - To reveal causative agent in pathological material during 5 hours
  - To detect medicamentous resistance (to streptomycin);
  - All listed above
7. What are the advantages of GenExpert system?
- Extraction of DNA and amplification are conducted in the cartridge;
  - Possibility to contaminate materials by nonspecific flora distinctly limited;
  - At the same time revealed DNA of MBT and is detected sensitivity to rifampicin during 2 hours;
  - The concordance of results with PCR, BACTEC, culture on Levenstein-Yensen medium in 97%.
  - All listed above
8. Which method of investigation of pathological material allows conducting specific identification of nontuberculous micobacteria?
- DNA-strip (HAIN-test);
  - BACTEC;
  - PCR;
  - Colorimetric method;
  - Bloody agar.
9. What kind of identification of MBT allows to distinguish mycobacterium of tuberculous complex from nontuberculous micobacteria?
- Bloody agar
  - Tuberculin skin test
  - Ziehl-Neelsen staining
  - All listed above
  - Non of the above
10. BACTEC MGIT 960 allows:
- To perform automatic monitoring of MBT grows;
  - To receive significant results during 5-14 days;
  - To keep up an automatic control under investigation quality;
  - To carry out up to 8000 of tests per year with the investigation of different pathological materials, except for blood;
  - all listed above
11. What are the advantages of the PCR (NAA)?
- Rapidity of analysis conduction (during 1-2 days);
  - High specificity and sensitivity;
  - Allows to control the effectiveness of chemotherapy at the patients with negative result of bacterioscopy;
  - B and C
  - All of them are correct
12. Which method of investigation of pathological material allows to conduct specific identification of nontuberculous micobacteria?

- A. Mass-spectrometry;
- B. BACTEC;
- C. PCR;
- D. Colorimetric method;
- E. Bloody agar.

13. What features are typical for micobacteria of tuberculous complex?
- A. Slow rate of growth (more than 3 weeks); expressed acid fastness coloration
  - B. The morphology of grown colonies (R-rough or S- smooth);
  - C. An optimal growth temperature 35-37 C;
  - D. Nonpigmented (creamy white color);
  - E. All answers are correct

Correct answers: 1.E, 2.E, 3. E, 4. B, 5. A, 6.A, 7.E, 8.A, 9.E, 10. E, 11.E, 12.A, 13. E

### 8. Situational task for conclusive assessing of the final level of knowlege:

1. The patient of 32 years old fell ill acutely after super cooling 2 weeks ago. He has the complaints on the cough with the sputum, breathlessness, fever up to 38,5° C in the evening, sweating, general weakness. Multiple symmetrical lesions of moderate size and slight intensity with vague contours all over the lung fields were detected by x-ray examination. Thin-walled cavity with the diameter up to 3 cm was detected in 1-2 segments of the left lung. MBT are found in the sputum by bacterioscopy. It was revealed 25 colonies of MBT on solid media, which are resistant to rifampicin (according to the results of molecular-genetic HAIN-test). What is the level of likelihood of MDR TB?
- A. High level of likelihood of MDR TB
  - B. Low level of likelihood of MDR TB
  - C. Moderate level of likelihood of MDR TB
  - D. He has no risk for MDR TB
  - E. None of the above
2. A patient of 40 years old fell ill acutely after super cooling 2 weeks ago. He is suffering from HIV for 4 years. Now he has the complaints on coughing with sputum, pain in the chest, fever up to 37,9° C in the evening, sweating, general weakness. During x-ray chest examination a focus of pathological shadow with diameter of 5 cm with translucency in the right lung 2 segment was detected. This shadow is of moderate intensity with unclear uneven contours. MBT are not found in the sputum by microscopy. What is the laboratory methods for smear investigation have to be done for this case?
- A. Culture on liquid medium (BACTEC), Hain-test
  - B. Culture on solid medium and liquid media
  - C. Drug Susceptibility Testing to II line on solid medium
  - D. Trance bronchial lung biopsy
  - E. Culture on solid and liquid media, Hain-test
3. The case of pulmonary fibrous-cavernous tuberculosis of the left lower lobe was diagnosed in patient at the age of 51 years. The shrinkage of left lower lobe of lungs and displacement of mediastinum to the left are detected by x-ray examination. Thick-walled cavity on the background of the cirrhosis is present in 6<sup>th</sup> segment of the left lung. Fine intensive nodular lesions in the lower part of the left lung are seen at x-ray picture. It is known that the patient has chronic course of disease with multiple episodes of interrupted treatment with recurrent smear-positive results. What is the case management for this patient?
- A. To register the case as relapse of TB, Category 2
  - B. To register the case as treatment failure, Category 2
  - C. To register the case as treatment after interruption, Category 2
  - D. To register the case as other case of TB, Category 2
  - E. To register the case as intermittent TB case, Category 2

4. A patient of 32 years old fell ill acutely after super cooling 2 weeks ago. He has the complaints of coughing with sputum, breathlessness, fever up to 38,5° C in the evening, sweating, general weakness. Multiple symmetrical lesions of moderate size and slight intensity with vague contours all over the lung fields were detected by x-ray examination. Thin-walled cavity with the diameter up to 3 cm was detected in 1-2 segments of the left lung. MBT are found in the sputum by bacterioscopy. What is the kind of syndrome of lung pathology is it?
- Syndrome of ring shadow
  - Syndrome of disseminative shadow
  - Syndrome of focal shadow
  - Syndrome of nodular shadow
  - Syndrome of milliar shadow
5. The patient of 32 years old fell ill acutely after super cooling 2 weeks ago. He has the complaints on the cough with the sputum, breathlessness, fever up to 38,5° C in the evening, sweats, general weakness. Multiple symmetrical lesions of moderate size and slight intensity with vague contours all over the lung fields were detected by x-ray examination. Thin-walled cavity with the diameter up to 3 cm was detected in 1-2 segments of the left lung. MBT are found in the sputum by bacterioscopy. It was revealed 25 colonies of MBT on solid media, which are resistant to rifampicin (according to the results of molecular-genetic HAIN-test). What is the scheme of treatment in this case?
- Empirical use of standard MDR regimens (IV category) in intensive phase (8Z,K, Lfx, Pt, Cs), but remain the case in 1 category till the moment of receiving DST MBT (rapid liquid culture systems)
  - Empirical use of standard MDR regimens (IV category) in intensive phase (8HRSZ), but remain the case in 1 category till the moment of receiving DST MBT (rapid liquid culture systems)
  - Empirical use of standard MDR regimens (IV category) in intensive phase (8HRSZ), but remain the case in 2 category till the moment of receiving DST MBT (rapid liquid culture systems)
  - Empirical use of standard MDR regimens (IV category) in intensive phase (8HRSZ), but remain the case in 2 category till the moment of receiving DST MBT (rapid liquid culture systems)
  - Empirical use of standard MDR regimens (I category) in intensive phase (8HRSZ), but remain the case in 4 category till the moment of receiving DST MBT (rapid liquid culture systems)
6. Right sided caseous pneumonia was newly diagnosed in patient of 28 years old. Evaluate of the degree of abundance of bacterioexcretion if MBT in sputum were revealed by microscopy (more than 10 MBT in each visual fields) and by culture method - 100 MBT bacilli).
- Scarce bacterioexcretion
  - Moderate bacterioexcretion
  - Abundant bacterioexcretion
  - Constant bacterioexcretion
  - Neglected bacterioexcretion
7. The patient of 36 years old was in a contact with the patient on confirmed case of MDR TB. 3 last years he was not x-ray examined. During x-ray chest examination before getting job a focus of pathological shadow with diameter of 5 cm with translucency in the right lung 1,2 segment was detected. This shadow is of moderate intensity with unclear uneven contours. Blood test is normal. Physical findings are without significant abnormality. The diagnosis of tuberculosis is made. How you will register this case?
- Cat 3, low likelihood of MDR TB, empirical prescription of standard MDR regimens
  - Cat 2, middle likelihood of XDR TB, empirical prescription of standard MDR regimens according to DST of source.
  - Cat 1, middle likelihood of MDR TB, empirical prescription of standard MDR regimens
  - Cat 1, higher likelihood of MDR TB, empirical prescription of standard MDR regimens according to DST of source.
  - Cat 4, higher likelihood of MDR TB, empirical prescription of standard MDR regimens
8. The patient (43 years) takes the course of chemotherapy at antiTB department with the upper right lobe disseminative TB, phase of cavitation and infiltration, Destr +, MBT+, M-, C+, Resist I-, Resist II 0,

Hist 0, Cat 1, Coh1(2013). The treatment with standard chemotherapy of isoniazid 0,3+ rifampicin 0.6+pyrazinamide 2.0+ ethambutol 1.2 was prescribed during intensive phase. 2 months later bacilli excretion remains the same. A positive sputum smear at the end of the intensive phase may indicate:

- A. the initial phase of therapy was poorly supervised and patient adherence was poor;
- B. doses of anti-TB drugs are below the recommended range;
- C. resolution is slow because the patient had extensive cavitation and a heavy initial bacillary load;
- D. the patient may have drug-resistant *M. tuberculosis* that is not responding to first-line treatment
- E. all listed above are correct.

9. The patient of 32 years old fell ill acutely after super cooling 2 weeks ago. He has the complaints on the cough with the sputum, breathlessness, fever up to 38,5° C in the evening, sweats, general weakness. Multiple symmetrical lesions of moderate size and slight intensity with vague contours all over the lung fields were detected by x-ray examination. Thin-walled cavity with the diameter up to 3 cm was detected in 1-2 segments of the left lung. MBT are found in the sputum by bacterioscopy. It was revealed MBT on solid media, which are resistant to rifampicin and isoniazid (according to the results of BACTEC MGIT 960). What is the category number?

- A. Category 4, with treatment more than 12 months.
- B. Category 2, with treatment more than 12 months.
- C. Category 2, with treatment more than 12 months.
- D. Category 2, with treatment less than 12 months.
- E. Category 1, with treatment less than 12 months.

10. The patient 40 years was admitted at the antiTB dispensary with the complaints on the cough with the sputum, raised body temperature up to 37,3C, weakness. For the first time pulmonary TB was revealed 4 years ago. After successful treatment the patient made the clinical recovery. The patient was well during 3,5 years. But now infiltrative shadow of non-homogenous structure was found in the left upper lobe by the chest X-ray examination. MBT were revealed by microscopy. What is the judgment for this case?

- A. To register in II category as “interrupted treatment”.
- B. To register in I category as “likelihood of MDR TB”.
- C. To register in II category as “likelihood of MDR TB”.
- D. To register in II category as “treatment failure”.
- E. To register in II category as “other TB case”.

**Correct answers:** 1.A,2.E,3.D,4.B,5.A,6.C,7.D,8.E,9.A,10.C

## 9. Recommended references:

### Main literature:

1. Phthisiology. A textbook for students / Petrenko V.I., Kyiv.-“Medicine”.- 2008. – 287 p.
2. Phthisiology. A teaching manual in Ukrainian and English / Pyatnochka I.T., Ternopol. – “Ukrmedknyha”. - 2002. – 257 p.

### Additional literature:

1. Clinical Tuberculosis. / J.Crofton, N.Horne, F.Miller, NewDelhi (India) – 1995. – 210.
2. Treatment of tuberculosis. Guidelines for national programmes. Fourth addition/ World Health Organization. – 2010. – 77 p.
3. Policy Framework for Implementing New Tuberculosis Diagnostics/ World Health Organization. – 2011. – 77 p.

Methodical recommendation is composed by: A.I.Choporova

Methodical recommendation is revised and proved on counsel of department: Phthisiology and Pulmonology

With addition (changes) \_\_\_\_\_

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Head of the department: professor

O.S. Shevchenko