SUSPICION CRITERIA AND RECOMMENDED EXAMINATIONS FOR THE EARLY DIAGNOSIS OF TUBERCULOSIS

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Abstract: *The incidence of tuberculosis (TB) in Romania is among the highest in Europe. Early detection and vigilance for extended diagnosis of TB are parts of the general objectives of the "National Strategy for Control of Tuberculosis 2007-2011". Active TB screening performed on the whole population is impossible to perform. According to the WHO requirements, active detection is performed only in case of high risk groups. In case confirmation is missing, the diagnosis is established on suspicion criteria for the diagnosis of TB, including: epidemiological criteria, clinical criteria, radiological criteria, tuberculin testing and QuantiFERON TB Gold testing. Early TB detection can be improved by efficiently informing the family physicians about the TB symptoms, so that they can refer the patients as early as possible to specialized examinations at the Pulmonology and Phtysiology Clinics.*

Cuvinte cheie: *criterii de suspiciune în diagnosticul tuberculozei, depistarea activă a tuberculozei, Strategia Naţională de Control al Tuberculozei 2007-2011*

Rezumat: *Incidenţa tuberculozei (TB) în România se plasează pe primele locuri din Europa. Depistarea precoce şi vigilenţa pentru diagnosticul cât mai larg al TB fac parte din obiectivele generale ale „Strategiei Naţionale de Control al Tuberculozei 2007-2011". Pe populaţia generală este imposibil de realizat depistarea activă a tuberculozei şi se face conform reglementărilor Organizaţiei Mondiale a Sănătăţii numai la grupele cu risc crescut. Confirmarea bolii se realizează în unităţile medicale specializate pe baza criteriilor absolute care confirmă diagnosticul de TB. În absenţa confirmării, diagnosticul se stabileşte pe baza criteriilor de suspiciune, care cuprind criterii epidemiologice, clinice, radiologice, testul tuberculinic şi cel Quantiferon TB Gold (QFT-G). Ameliorarea depistării precoce a tuberculozei se poate face prin creşterea informării medicilor de familie cu privire la simptomele TB, pentru trimiterea cât mai rapidă a pacienţilor la investigaţii specializate în serviciile de pneumoftiziologie.*

Tuberculosis is still the most frequent infectious disease in the world. The incidence of tuberculosis (TB) in Romania is among the highest in Europe. Under these circumstances early detection of TB is an important priority that will:(2,6)

- on one hand allow for initiation of targeted therapy for healing the patient, and avoiding complications and death;
- on the other hand limit the spread of infection to contacts of the index case.

In 2006 the WHO deployed the StopTB strategy with the aim of "A world without TB", and the proposed target is "The dramatic reduction of the global TB burden until 2015", according to the "Millennium Development Goals" (MDG) established by the UN.(1)

The general objectives of the Strategy of Romania are defined according to the MDG and aim at achieving the goals established by the StopTB Partnership:(1,2)

- Maintaining the 100% DOTS **(Directly Observed Therapy in Short course)** coverage of the TB population;
- Maintaining a level of detection of at least 70% of the total of existing TB cases until 2011;
- Achieving and maintaining a therapeutic success rate of at least 85% of the total of new bacteriologically confirmed pulmonary TB cases until 2011.

Early detection of TB is difficult to achieve, as the disease is characterized for a long period of time by unspecific symptoms that are not noticed by the patients or they are considered to be signs of other conditions: fatigue, stress, smoking, and consequently the patients will not seek medical attention.(19)

Active TB screening performed on the whole population is impossible to perform due to certain objective factors related to the following: harmful effects of X-rays (if the radiologic examination would be repeated frequently); the impossibility to perform repeated (every 1-2 months) clinical and radiological examinations of the whole population, and high costs without diagnostic efficiency.(17,19,1) According to the WHO requirements, active detection is performed only in case of high risk groups.(1-6)

TB can occur in pulmonary and extrapulmonary clinical forms in children and adults. Based on the natural history of the disease there is primary TB (occurring in children and young adults with non-sensitized organism that is naïve to the Koch bacillus - KB) or secondary TB (occurring in organisms sensitized by a first infection, following a variable timeframe).(17,19) In case of all types of TB there are common criteria for suspicion and confirmation of diagnosis.

Confirmation of TB is performed at Pulmonology and Phtysiology medical facilities (outpatient or inpatient departments), with the contribution of bacteriology and pathology laboratories.

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As the family physician has the most extensive contact with the population, he will be referring suspected patients as soon as possible to specialized institutions to continue the examinations for the diagnosis of TB.

The 2 absolute criteria confirming the diagnosis of TB are(17,19)

- Positive bacteriology testing for the KB in different samples (microscopy – Ziehl-Neelsen staining and colony growth on Löwenstein-Jensen culture)
- Positive histopathology examination (presence of TB specific granulomas in biopsy tissues or in surgical samples).

In case confirmation is missing, the diagnosis is established by correlating certain high probability criteria that have to be well-known, considering the variety of bacteriologically negative forms, delayed positivity of KB cultures (1 to 3 months), and in some cases the lack of a histopathology examination (extrapulmonary TB, or TB localized in organs where biopsy cannot be performed).

Suspicion criteria for the diagnosis of TB are:(12,13,17,19)

1. Epidemiological criteria
2. Clinical criteria
3. Radiological criteria
4. Tuberculin testing
5. QuantiFERON TB Gold testing

1. Epidemiological criteria

Medical history and the clinical examination raise the suspicion of TB by evidence of exposure to a contagious source that eliminates bacilli:

- Positive family history or prolonged contact with a patient represents the existence of an exogenic source;
- Personal medical history of TB may be suggestive for a new TB episode (through reactivation of germs remaining from the first episode);

Demonstration of risk factors of immunodepressive potential increases the probability of catching or reactivation of TB infection. Risk factors contributing to TB disease are internal and external:

Internal factors:(19)

- Very young or very old age when there is an immunodeficiency; male patients;
- Preexisting diseases and conditions: HIV infection/AIDS, silicosis, chronic hepatitis and hepatic cirrhosis, chronic tobacco use, chronic alcoholism, renal failure, gastrectomies and malabsorbtion syndromes, malignant tumors and hematologic diseases, collagenoses, treatment with immunodepressant drugs;
- Preexisting TB infection.

The **external, environmental factors** are: climate, atmospheric pollution, economic conditions (inadequate nutrition – whether composition or quantity); housing – crowded, unhygienic, moist; low family budget, low cultural levels, difficult working conditions with noxae, commuting, alcoholism, tobacco use, drug addiction, deficient anti-tuberculosis fight, natural disasters, migrations, wars).(19)

Highlighting all these epidemiological aspects has to be performed for all patients, regardless of the consulting physician's specialization. The patient with risk factors and symptoms will be referred to pulmonology consultation. As result, the number of actively identified cases increases with a distinct contribution from primary care medicine and other specialties, and the number of unknown bacillus sources decreases.(18)

2. Clinical criteria

The clinical examination is the most simple and cost effective means for TB diagnosis. The clinical examination performed by the general practitioner will allow him to raise a diagnostic suspicion, which will result in referring the patient for targeted investigations in specialized facilities. TB has symptoms that upon correlation and placing into epidemiological context will determine confirmation examinations.

General symptoms – the bacillus impregnation syndrome comprises: asthenia, sweating – especially nocturnal, loss of appetite, weight loss, subfebrility, paleness, fatigue. The symptoms are unspecific, but display properties that should raise the suspicion of TB: insidious start, uneventful and slow evolution; the symptoms may occur isolated or grouped. The patient's condition does not improve after vitamin administration or unspecific antibiotic or anti-inflammatory treatment. Sometimes symptoms are missing or are lost between the symptoms of another underlying disease – HIV/AIDS. In such cases the most important criterion will be the radiologic examination.(9,10,14)

Differentiation from other diseases with similar symptoms has to be made: viral hepatitis, acute poliarticular rheumatism, tumors with neoplastic impregnation, hyperthyroidism, chronic focal infections, hematologic or immunologic diseases.(12,13)

Local symptoms, characteristic to the involved organ

a) Pulmonary TB (2,12,17)

- Prolonged coughing (2 to 3 weeks) that does not respond to antitussive or antibiotic treatment;
- The discharge is low in quantity, it is mucous, adherent, muco-purulent, non-fetid.
- Rarely blunt and localized chest pain;
- Dyspnoea in more advanced stages, when the patient is commonly bacteriologically positive;

In case of pediatric TB the local symptoms may be missing, and in such a case, if any suspicion of TB arises, besides epidemiological criteria and radiologic examination, morning gastric fluid sampling is recommended for detection of swallowed KB.(8)

In case of HIV patients, where bacteriology is rarely positive, coughing associated with fever of any duration and nocturnal sweating have a high sensibility (93%) and specificity (33%) for TB.(14)

These symptoms or suggestive conditions are the following:(12)

- Uncontrolled diabetes;
- Unjustified amenorrhea;
- Hemoptysis, especially in young people (in elderly and smokers it is suggestive of a bronchopulmonary neoplasm);

b) Osteoarticular TB:(17,19)

- The pain is strongest in a fixed area; it increases upon pressure, movement, and it is especially nocturnal. It irradiates along the nerves and improves during rest and immobilization;
- It is associated with other signs: swelling of the region with periarticular edema and pale skin, functional failure of the articulation, vicious antalgic positions, muscular hypertrophy;

- Fistulas or wandering abscesses develop that will evacuate yellowish caseum at a certain distance.

c) Secondary lymph node TB:(13,19)

- Lymph node TB most commonly starts in the lateral cervical region (90%), at the angle of the mandible as an inflamed lymph node group;
- Initially the lymph nodes are soft and isolated, then the process will engage other nearby nodes (pseudotumor aspect); subsequently liquefaction occurs and fistulae develop to the surface; sometimes caseous pus is discharged through the opening of the fistula. The fistula may close spontaneously resulting in a retracted scar.
- The involved lymph nodes are in different stages of evolution, some are soft, others are already fistulized, and others are hard and scarred. Multiple fistulae may develop – the clinical aspect of the skin is called "scrofuloderma".

d) Urogenital TB:(17,19)

- The **symptoms** are quiet for a long time: polakyuria, microscopic leukocyturia and hematuria The symptoms become evident when the caseous lesions open up towards the urinary pathways: permanent, imperative polakyuria, especially nocturnal; the urine becomes turbid, reddish, and voiding pain and bladder tenesmus develops.
- **Genital TB symptoms in males:** polakyuria, bladder tenesmus, perineal and rectal pain, hematuria, scrotum pain. Untreated, chronic TB orchiepididymitis will be accompanied by hydrocele or fistulization to the skin. Differential diagnosis has to be made with proliferative prostate conditions or urinary calculi. The patients will be referred to urology clinics.
- **Genital TB symptoms in females:** pain of the adnexes, and frequently sterility, extrauterine pregnancies or abortion can occur as a result of inflammation and stenosis.

e) Pericardial TN – insidious start with bacillary impregnation syndrome, precardiac pain, and irritating cough. The apex beat is inside the area of the cardiac dullness, cardiac sounds are dimmed, and the pulse is paradox (higher frequency during expiration). More rarely, the evolution is acute, with sudden development of cardiac tamponade symptoms and arterial hypotension, superior vena cava compression (facial edema and cyanosis, turgescent jugulars) and antidyspneic positions.(20)

f) Digestive TB (19,21)

General signs of bacillus impregnation;

- Anorexia, nausea, inconstant vomiting, meteorism;
- Vague abdominal pain, especially after meals or sharp pain in case of occlusive complications (through intestinal loop adherence and agglutination);
- Bowel movement disorders – constipation or diarrhea (subocclusion through intestinal stenosis);
- Palpation of certain abdominal masses, associated ascites, hepatomegalia, mesenteric lymphadenopathy;
- Hippocratic fingers, cachexia;
- Pathologic stools with mucus, caseous material and blood;
- Peritoneal or enterocutaneous fistulae.

Peritoneal TB: constipation, the abdomen in concave with painful contraction of its wall; sometimes a "tumor mass" or "mesenteric cord" is palpated; there are frequent occlusive complications. Development of ascites will lead to meteorism, and upon percussion dullness is heard (fluid) that will form cysts over time.

g) Pleural TB (12,16)

- Chest pain, sometimes stabbing pain, dyspnea in case of large effusions, dry cough;
- Dimming of the normal respiratory sounds, dullness or partial dullness, sometimes pleural rub at the time of onset;

h) Adrenocortical TB (7,12,19)

- Asthenia, anorexia;
- Weight loss;
- Nausea, abdominal pain;
- Diarrhea, dehydration;
- Depression, irritability, decrease of concentration;
- Hyperpigmentation of the skin and mucous membranes;
- Loss of body hair, especially in the axillary and pubic region;
- Arterial hypotension <110 mmHg.

3. Radiologic examination and other imaging studies

Imaging studies are highly suggestive for TB detection, but alone they do not provide confirmation of active TB (differentiation from sequelae is necessary). TB suspicion will be followed by referring the patient to specialized facilities that are linked to a laboratory for performing under adequate circumstances the bacteriology testing and histopathology examination, if needed.

The most used **imaging methods** in TB diagnosis are:

- **Standard chest X-ray** – postero-anterior and lateral;
- Computed tomography (CT) is used especially in extrapulmonary TB or in cases where routine clinical and radiological examinations do not allow diagnostic differentiation between TB and other lesions (tumors, bronchiectasis, abscesses, cysts, encapsulated pleural effusions);
- **MRI** – rarely used;
- **PET-CT (positron emission tomography)** – rarely used for differentiation from tumors;
- **Ultrasound examination;**
- Thoraco-pleuro-pulmonary and mediastinal TB: chest X-ray, chest CT scan, cervical and thoracoabdominal ultrasound, echocardiography;

Bone and osteoarticular TB: X-ray, CT scan, PET-CT (positron emission tomography), MRI, ultrasound examination of the joint**;**

Urogenital TB: urography, hysterosalpingography, abdominal and scrotum ultrasound examination, abdominal and genital CT scan

Lymph node TB: ultrasound examination and CT scan;

Digestive TB: contrast enhanced X-ray, abdominal ultrasound examination, abdominal CT scan;

Nervous system TB: cranial CT scan, MRI

4. Tuberculin skin test

The tuberculin test (IDR2PPD) is a test for detecting TB infection and the "allergic" condition (cell mediated, type IV late hypersensitivity, according to the Gell and Coombs classification of immune reactions). The tuberculin test is based on the capacity of the previously (1 to 2 months before) sensitized (by a first tuberculosis infection) organism to respond by a lymphocyte and macrophage mediated allergic reaction to a new administration of bacillus protein antigens (tuberculin). Tuberculin allergy is a "suprainfection", and will persist as long as there are living KB (even dormant) in the body.(11,17)

The induration is evaluated after 72 hours, and it is pink-pale, rarely comprising a blister and necrosis, well circumscribed and elevated from the surrounding skin.

Positive reactions are ≥ 10mm, those between 10 and 17 mm are normal reactions, and those > 17mm are hypersensitivity reactions.(2,17) Negative reactions are ≤ 9mm: a 0 mm reaction = no response, and reactions between 0 - 9mm are low sensitivity reactions (in this case the reaction is caused by the BCG vaccine, by infections with atypical germs, or very mild KB infections).

The hypersensitive people will be evaluated radiologically to exclude the active disease. Subjects with radiologic results suggesting TB will undergo bacteriology testing. Children and young adults between 10 and 35 years with hypersensitivity reactions, but a normal clinical and radiological examination will receive chemoprophylaxis with Isoniazid 7/7, 5mg/kg for 6 months. In case of HIV+ people, the IDR2PPD is considered hypersensitive from values >5mm, and if e.g. radiology and bacteriology testing exclude an active TB, 12 months chemoprophylaxis will be introduced.

Interpretation of the tuberculin test (17,19)

- A **positive reaction** shows that the subject is infected and sensitized to living BK antigens, through a cell mediated, type IV late hypersensitivity. A positive reaction does not provide information on whether the infected subject is healthy or not.
- A **negative reaction** shows the lack of certain responses to BK Ag. This lack of response demonstrates whether the lack of infection, or the 4 to 8 week long pre-allergic period, or an inhibition of the immune response caused by immunodepressive conditions: treatment with corticosteroids and cytostatic drugs, radiation therapy, viral hepatitis, HIV infection/AIDS, typhoid fever, mycoses, malignant tumors and hematologic diseases, chronic renal failure, diabetes mellitus, cachexia; older age, severe advanced TB.(19)

Indications of the tuberculin test (2)

TB diagnosis – individual testing:

- In case of children and young adults for diagnosis of primary TB;
- Additional in the diagnosis of extrapulmonary TB;

Mass PPD testing for the following groups of children and young adults:

- Groups of children scheduled for BCG vaccination (at 6 months 1 year);
- Contacts from 0 to 35 years in the infection area;
- Children admitted to the pediatrics or infectious diseases departments, including HIV;(5,8,11)

Contraindications of tuberculin testing are as follows: patients with confirmed active TB, ongoing infectious and eruptive diseases, febrile conditions, recovery after severe infectious diseases;

5. QuantiFERON TB Gold

QuantiFERON TB Gold (QFT-G) is an „in vitro" assay measuring the level of a component of cellular immunity – interferon (IFN-γ). It is used as a diagnostic method of latent TB, and as an additional test for certain forms of the active disease. The bacteriology testing of the expectoration and chest X-ray are necessary to differentiate latent TB infection and active disease. In Europe a similar test is also used, called T – SPOT TB (ELISA test).

QFT-G does not replace PPD testing, it supplements it. It detects IFN-γ release into the blood by activated T lymphocytes in previously sensitized people. The blood is incubated with "bacillus" antigens. Synthetic proteins are used that are similar to the M. tuberculosis or M. bovis Ag. „Early secretory antigenic target" - 6 (ESAT-6) or „Culture filtrate protein - 10 (CFP-10). As these proteins are missing from the BCG vaccine bacillus and the majority of atypical mycobacteria, it is expected that the test will be more specific for the diagnosis of Myocbacterium tuberculosis infections.

Advantages of the Quantiferon test:

- It requires only one visit to the clinic (IDR2PPD needs 2 visits), and the results are available within 24 hours;
- It does not cause "booster" effects (sensitization and enhancement of response) upon repeating the test;
- There are no false results (in case of IDR2PPD there is a subjective interpretation of the induration);
- It will not yield positive results in case of recent BCG vaccination, or MNT infections.(15)

Disadvantages of the Quantiferon test:

- It needs phlebotomy and processing within 12 hours;
- There is limited information about the use of QFT-G in children under 17 years, people recently exposed to TB and people with major immune deficiencies (HIV/AIDS, chronic treatment with cortisones or cytostatic drugs, malignant hematological diseases, silicosis, diabetes or chronic renal failure).(8,14)

A positive QFT-G test prompts the performance of certain examinations (15) clinical examination, and chest and bone X-ray, HIV testing (5,10) bacteriology testing, histopathology testing, based on the clinical suspicion of extrapulmonary TB. If these examinations confirm the presence of the disease, antitubercosis therapy should begin. If no disease is present and the test is positive, chemoprophylaxis has to be performed in people with high risk of developing the disease. A negative test with no disease present indicates a latent TB infection, and does not require subsequent examinations. In case of a negative QFT-G, with recent contact with bacillus-eliminating patients, the test should be repeated at > 8-10 weeks (as for PPD).

Patients under 5 years or immunodepressed, with recent contact with bacillus-eliminating patients and negative QFT (they are in the "no response window") need chemoprophylaxis and epidemiologic, clinical, radiological or bacteriological follow-up in order to exclude the disease. Chemoprophylaxis should be continued even if QFT is still negative at 8-10 weeks.(5,15)

REFERENCES

1. StopTB (www.stoptb.org).
2. Programul Național de Control al Tuberculozei în România 2007-2011 M.S.București; 2006.
3. World Health Organization. Global tuberculosis control 2008: surveillance, planning, financing. Publication no.WHO/HTM/TB/2008.393.
4. World Health Organization. Green Light Committee Initiative annual report. Publication no. WHO/HTM/TB/2008.409.http://www.who.int/tb/challenges/mdr/ greenlightcommittee/en.
5. World Health Organization. Tuberculosis infection control in the era of expanding HIV care and treatment: addendum to WHO guidelines for the prevention of tuberculosis in health care facilities in resource-limited settings, World Health Organization; 2006.

6. Wallace RM, Kammerer JS, Iademarco MF, et al. Increasing proportions of advanced pulmonary tuberculosis reported in the United States: are delays in diagnosis on the rise? Am J Respir Crit Care Med. 2009;180:1016-1022.
7. Williams GH, Dluhy RC. Disorders of the adrenal cortex. In: Braunwald E, ed. Harrison's Principles of Internal Medicine. 17th Ed. New York: McGraw-Hill Professional; 2008. p. 2247-2268.
8. Wilson ME. New Approaches to Diagnosing Pediatric Tuberculosis. Infectious diseases, apr, 2010; Reviewing: Oberhelman RA et al., Lancet Infect Dis. 2010 Jul 26.
9. Agizew TB, Arwady MA, Yoon JC, et al. Tuberculosis in asymptomatic HIV-infected adults with abnormal chest radiographs screened for tuberculosis prevention. Int J Tuberc Lung Dis. 2010 Jan;14 (1):45-51.
10. AIDS epidemic update. Biroul regional SIDA, Copgenhaga, December 2007.
11. Biselli R, et al. Distinguishing Active from Latent Tuberculosis. Clin Microbiol Infect. 2010 Aug;16:1282.
12. Bogdan MA, Corlan E. Tuberculoza. Pneumologie. Ed. Univ. Carol Davila, Bucureşti; 2008. p. 133- 167.
13. Broaddus VC, Light RW. Tuberculosis. In: Mason RJ, Murray J, Broaddus VC, Nadel JA. Textbook of Respiratory Medicine. 4th Ed, WB Saunders; 2005. p. 979-1044.
14. Cain KP, McCarthy KD, Heilig CM, Monkongdee P, et al. An algorithm for tuberculosis screening and diagnosis in people with HIV. N Engl J Med. 2010 Feb 25;362:707-716.
15. Cummings KJ, Smith TS, Shogren ES, Khakoo R, et al. Prospective comparison of tuberculin skin test and QuantiFERON-TB Gold In-Tube assay for the detection of latent tuberculosis infection among healthcare workers in a low-incidence setting. Infection Control & Hospital Epidemiology. 2009 Nov;30(11):1123-1126.
16. Jimborean G, Simon K, Platon A. Aspecte ale tuberculozei pleurale în jud. Mureş (1994-1999). Rev de Medicină şi Farmacie, UMF Tg.Mureş. 2000(46);1:104-107.
17. Jimborean G, Ianosi ES. Tuberculoza. Micobacteriozele atipice. Elemente de diagnostic şi tratament. Ed. Univ. Petru Maior, Târgu-Mureş; 2004.
18. Lam PK, LoBue PA, Catanzaro A. Clinical diagnosis of tuberculosis by specialists and non-specialists. Int J Tuberc Lung Dis. 2009 May;13(5):659-661.
19. Jimborean G, Ianosi ES. Tuberculoza pulmonară şi extrapulmonară – UniverstiyPress; 2010.
20. Reuter H, Burgess L, van Vuuren W, Doubell A. Diagnosing tuberculous pericarditis. QJM. 2006;99:827.
21. Pereira JM, Madureira AJ, Vieira A, Ramos I. Abdominal tuberculosis: Imaging features. European Journal of Radiology. 2005;55(2):173-180.
22. Harisinghani M, McLoud TC, Shepard JA, Ko JP, Shroff MM, Mueller PR. Tuberculosis from head to toe. Radiographics. 2000;20:449-470.