ACTIVE TUBERCULOSIS

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Updated ALD Guides and Lists

Guides for doctors developed by HAS are revised every three years.

In the meantime, the list of procedures and services (LAP) is revised, at minimum, on a yearly basis. This list is available on the HAS website.

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1. Introduction

Tuberculosis (TB) is an infectious disease, caused by the *Mycobacterium* bacillus of the *tuberculosis* complex which is mainly transmitted from person to person by the aerial route. The pulmonary form predominates (71.5% of cases in 2004) but all organs may be affected. Tuberculosis is a disease that is curable provided that an internationally standardized treatment regimen comprising an antibiotic combination is adhered to for a period of 6 months or more. The occurrence of multi-drug resistance (resistance to at least isoniazid and rifampicin) makes management more complex as other drugs are not very effective and cause numerous adverse effects.

France is a country with a low incidence: 5,512 cases of tuberculosis, including 452 cases in children aged less than 15 years, were reported in 2004 according to the mandatory reporting procedure (estimated exhaustiveness of 65%). The incidence rate of reported cases is falling (9.2 cases per 100,000 inhabitants in Metropolitan France) but this fall varies considerably according to region or population. Multi-drug resistance rates have remained stable despite an increase in 2002, with a prevalence of more than 1% for the first time for 10 years (1.4%).

Cases of tuberculosis are concentrated in the Ile-de-France region and French Guiana where incidence rates are three times the values elsewhere (20.8/10^5 and 32.5/10^5 respectively). The main high-risk groups are immigrants from countries with a high prevalence, the homeless, elderly, HIV-infected individuals and prison detainees. Tuberculosis primarily afflicts socio-economically deprived or excluded persons as well as those with other conditions with a high morbidity (particularly high incidence of drug-addiction, alcoholism and HIV-co-infection).

This guide is intended to be a pragmatic reference tool for doctors managing active tuberculosis. Its content has been discussed and validated by a multidisciplinary working group. It is a practical summary of current clinical practice guidelines, consensus conference recommendations, and expert opinion (when there were no relevant data to draw guidelines). Expert opinion is needed in fields such as patient follow-up, where the pattern of surveillance is based on consensus among professionals rather than on comparative data from clinical trials. The proposed treatment plans have been reviewed by AFSSAPS\(^1\).

An ALD guide cannot be comprehensive, i.e. cover all comorbidities, hospital care protocols, etc. It does not claim to cover all the ways in which active tuberculosis may be managed, nor does it a discharge doctors from their responsibility to their patients. It just describes the basic framework of care for patients with uncomplicated tuberculosis. It will be updated as new data are validated.

\(^1\) AFSSAPS: French Healthcare Products Safety Agency
2. **Initial assessment**

2.1 **Objectives**

- Rapidly establish a diagnosis for early institution of treatment.
- Evaluate the risk of secondary cases and isolate patients accordingly.
- For a patient with a high index of suspicion of tuberculosis, laboratory confirmation by demonstration of tuberculosis bacilli (*Mycobacterium tuberculosis*, *M. bovis* ou *M. africanum*).
- Evaluate the different sites of the disease.
- Seek contraindications to certain antitubercular treatments.
- Collect data about resistance to antitubercular drugs.
- Evaluate factors that may impact adherence to treatment.
- Mandatory reporting: report the case to the health authorities as rapidly as possible in order to initiate follow-up of close contacts and send the printed notification form for epidemiological monitoring (Appendix 1).

2.2 **Professionals involved**

The diagnosis of tuberculosis may be made by any doctor. A specialist medical opinion is recommended.

The doctor must base his evaluation on all the necessary resources and in particular those of the social services and tuberculosis control centres (CLAT).

2.3 **Summary of initial assessment**

► **Clinical examination**

- Seek:
  - History of current illness;
  - Past medical history including, in particular, previous antitubercular treatment (risk of increased resistance);
  - Epidemiological context (geographical origin or possible tuberculosis exposure or travel in a country with endemic tuberculosis during the last 2 years);
  - General signs (wasting, asthenia, anorexia, prolonged fever, night sweats);
  - Respiratory clinical signs (cough, dyspnea, expectoration, haemoptysis, chest pain);
Extrapulmonary signs (fluctuating adenopathy, spinal or osteo-articular pain, meningeal syndrome, epididymal involvement, etc).

 ► **Radiological workup : remettre sous la forme initiale avec des points**

- Chest radiography
  - All patients, including those with an extrapulmonary form

- Chest CT-scan
  - Reserved for complex forms with the x-ray cannot be correctly interpreted; not often useful in pulmonary tuberculosis; may be useful in lymph node tuberculosis, complex pleural lesions on in children

- Extrapulmonary imaging
  - Essential to establish the diagnosis and the repercussions of extrapulmonary forms

 ► **Bacteriological workup to be prescribed**

- Evaluation of acid fast bacilli (AFB) smears by microscopic examination and culture:
  - In the case of suspected respiratory tuberculosis:
    - On 3 samples, preferring spontaneous sputum samples,
    - In persons unable to produce sputum, the test may be carried out on stomach contents obtained by gastric intubation or on induced sputum samples,
    - After 3 negative samples, the test is carried out during fiberoptic bronchoscopy (aspiration of bronchial secretions);
  - In the case of a suspected extrapulmonary form:
    - Suspected renal tuberculosis: urine samples only if aseptic leukocyturia,
    - Suspected tubercular meningitis: cerebrospinal fluid sample by lumbar puncture,
    - Disseminated tuberculosis in the event of severe immunodepression: blood culture,
    - Adenopathy: excision or puncture,
    - Other sites (pleura, peritoneum, bronchus, bone, pericardium, liver, etc): puncture or biopsy.

- Tests of sensitivity to standard antitubercular drugs.

- Gene amplification test: undergoing evaluation.
Intradermal reaction (IDR) to tuberculin in children

Blood assay of interferon γ

- To aid diagnosis of extrapulmonary forms of tuberculosis which are often difficult to define.

Histology

- Contributes to diagnosis: necessary when casein is present and suggested if non-necrotizing giant cell granulomas (in the absence of another cause) are present.

Laboratory investigations before initiating of treatment

- Complete blood count;
- Transaminases, bilirubin, alkaline phosphatases and gamma GT;
- Serum creatinine, sodium, uric acid;
- Screening serologic tests for HIV: proposed systematically because of comorbidity;
- Serologic screening for hepatitis B and C: proposed systematically as they frequently coexist with tuberculosis;
- This workup may be individually tailored for children.

Other examinations

- Ophthalmological examination with colour vision: before institution of treatment with ethambutol.
- Detection of pregnancy in women of child-bearing age, because of the contraindication for pyrazinamide. This may be done though interview (in particular date of last periods) and where necessary a qualitative pregnancy test.
3. Clinical management

3.1 Objectives

- Disclosure of diagnosis
- Institution of treatment as rapidly as possible in the patient's interest (faster cure and fewer sequelae) and to reduce the risk of contaminating close contacts.
- Mandatory notification of the patient (law n° 2002-303 of March 4, 2002: disease exposing others to a risk of infection). Patient information is crucial: Uninformed patients may change the treatment regimen, suppressing one or more drugs which they think are no longer necessary and thereby causing the treatment to fail or a relapse to occur; the patient must also be informed about mandatory recording and reporting procedures which involve an investigation of his/her close contacts.
- Patient education should involve the following items: nature and duration of treatment, adherence, modes of transmission of tuberculosis bacilli and its prevention, need for follow-up of contact subjects.
- Ensure access to treatment as well as follow-up both during and at the end of treatment.

3.2 Professionals involved

Treatment is instituted whenever possible by a practitioner experienced in the management of tuberculosis in order to check the safety of treatment and adherence. Continuity of care must be planned and defined, in particular between the primary care doctor and the practitioner.

The doctor should seek the opinion of any medical or ancillary medical professional where necessary.
3.3 Drug treatments

► Antitubercular treatment

- Standard antitubercular drug treatment in adults
  Six months of daily treatment in two phases comprising:
  - A first 2-month phase using a combination of 4 antibiotics: isoniazid (INH), rifampicin (RMP), pyrazinamide (PZA) and ethambutol (EMB);
  - Then during the second 4-month phase, combination of isoniazid and rifampicin.
  Combined pharmaceutical forms are recommended in order to promote adherence and reduce the risk of drug resistance.

- Standard antitubercular treatment in children
  Six months of daily treatment in two phases comprising:
  - A first 2-month phase using a combination of 3 antibiotics: isoniazid, rifampicin, pyrazinamide. The use of ethambutol is restricted to cases rich in bacilli or suspected to be caused by resistant bacilli;
  - Then for a second 4-month phase, combination of isoniazid and rifampicin.

- NB: take into account all drug interactions particularly when using rifampicin.

► Second-line treatment

These drugs are only prescribed after obtaining specialist opinion for multi-resistant or specific forms of the disease; some are obtained within the scope of a temporary use authorization (ATU) issued by Afssaps:

- Streptomycin
- Amikacin (outside Marketing Authorisation)
- Capreomycin (ATU)
- Ethionamide
- Protionamide
- Levofoxacin (outside Marketing Authorisation)
- Moxifloxacin (outside Marketing Authorisation)
- Cycloserine (ATU)
- Para-aminosalicylic acid (ATU)
- Linezolide (outside Marketing Authorisation)
- Thioacetazone (ATU)

2 ALD guides refer to drug classes without listing all the drugs indicated in the disease in question. Each drug is to be used only within the framework of its Marketing Authorisation. If for a specific reason this is not the case, and more generally, whenever a drug is prescribed in circumstances other than those given in the Marketing Authorisation, this is the sole responsibility of the prescriber, who must specifically inform the patient of this.
**Cases requiring referral to a team of specialists**
- The prolongation of treatment in certain extrapulmonary form, particularly neuromeningeal or in pulmonary tuberculosis with an unusual clinical course;
- After treatment interruptions;
- Relapse;
- Resistance to antitubercular drugs.

### 3.4 Other pharmacological treatments

- **Corticosteroids**
  These may be used in pericarditis, meningitis, milliary tuberculosis, cerebral tuberculoma and bronchial obstruction in children.

- **Vitamin B6**
  Systematic prevention of peripheral neuropathy caused by isoniazid in patients at risk (pregnancy, alcohol addiction, malnutrition, pre-existing neuropathy, renal insufficiency, HIV infection).

- **Dietary supplements**
  In the case of malnutrition.

### 3.5 Other measures

**Isolation of contagious patients**
- Evaluate the risk of secondary cases and plan patient isolation accordingly.
- All pulmonary, bronchial or laryngeal forms of tuberculosis are potentially contagious, whether the direct examination is positive or negative. Patients are still contagious until from 1 to 3 weeks after institution of treatment.

**Encourage adherence to treatment**
Set up the necessary conditions to promote adherence to treatment, with the help in particular of social services:
- Ensure that the conditions are in place for reimbursement of treatment costs (long-term illness status, universal health coverage, state medical aid, etc);
- Regularly identify obstacles to compliance (personal, family, administrative, financial, etc), and implement actions to provide social aid (administrative procedures, work, housing, allowances, etc) and medical support (treatment of addiction, psychiatric disorders etc);
• Implement health education by clinicians, nursing teams and patient associations in order to promote acceptability and adherence to treatment, or if necessary plan admission to an experienced medium-term stay unit;

• Report non-complying or suspected non-complying patients to tuberculosis control centres (CLAT);

• Use the means proposed within the scope of the national tuberculosis control program.

► **Ophthalmological examination with colour vision**
During the first months of ethambutol treatment.

► **Surgery**
Surgery may be indicated in multiresistant tuberculosis (disease caused by a strain of *M. tuberculosis* resistant to at least isoniazid and rifampicin) with small, limited lesions, for which the number and type of resistance to antitubercular agents suggest that a cure may be impossible or in the case of treatment of complications or sequelae.
I. Follow-up

4.1 Objectives

- Cure the patient;
- Avoid spread of the disease by an irregularly treated patient and the development of resistance to antitubercular drugs;
- Ensure patient follow-up until the disease is cured and document the end of treatment.

To reach these objectives follow-up must:

- Check that patients adhere to therapy;
- Ensure that treatment is dispensed without interruption throughout its duration;
- Set up supervised treatment (DOT: directly observed therapy) where necessary with the assistance of community care structures (tuberculosis control centres, outreach workers, etc) in the case of non-adherence, resistance to treatment, relapse, problems understanding treatment, incapacity, homeless or alcoholic patients.
- Find and treat TB complications and the adverse effects of treatment;
- Verify recovery according to following criteria: sensitive mycobacteria, six months of appropriate treatment, good adherence, disappearance of clinical signs and regression of reversible radiological signs;
- Qualify treatment outcomes for each patient according to opinion of the French National Public Health Council (CSHPF) of June 2006 (Appendix 2).
4.2 Professionals involved

- Patient management involves the primary care physician, hospital team, specialists, tuberculosis control centres (CLAT), community doctors [occupational and school doctors, maternity and infant care services (MIP), prison outpatient units (UCSA), residential care coordinator for dependent elderly persons (EHPAD)], ancillary health workers and social workers.

4.3 Frequency of visits

Clinical visits are recommended at least:

- 10 to 15 days after initiation of therapy;
- Then at 1, 2, 4, 6, 9, 12 and 18 months.

4.4 Complementary examinations

- **Chest X-ray**
  To be performed at least:
  - During the second month of treatment;
  - At the end of treatment;
  - 18 months after the start of treatment of a tuberculosis disease.

- **Bacteriology**
  Essential follow-up to confirm the sterilization of lesions.
  Bacteriological monitoring (direct examination and culture) comprises:
  - Early bacteriological examination between day 10 and day 15 of treatment indicated in patients with a positive smear;
  - Then after 2 months and 6 months.

- **Ophthalmological examination**
  A second eye examination must be performed during the second month of ethambutol treatment and further examinations are performed every two months in the exceptional case of prolongation of ethambutol treatment (after obtaining the opinion of the team of specialists).
Appendix 1. Mandatory reporting form

Cerfa Form 12210*01 *mandatory tuberculosis reporting* may be downloaded from the website of the French Institute for Public Health Surveillance: [http://www.invs.sante.fr/surveillance/mdo/fiches/fiche_tuberculose.pdf](http://www.invs.sante.fr/surveillance/mdo/fiches/fiche_tuberculose.pdf)

Criteria for notification of tuberculosis disease:
- **Confirmed Case:** Disease due to a mycobacteria of the *tuberculosis* complex confirmed by culture
- **Probable Case:**
  1. Clinical and/or radiological signs compatible with tuberculosis
     *and*
  2. Decision to treat the patient with a standard antitubercular treatment
## APPENDIX 2. TUBERCULOSIS TREATMENT OUTCOMES

The advise of the French counsil on public hygene

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<th>Definition of treatment outcome categories</th>
<th>Complementary information to be collected</th>
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| Completed treatment (the patient took at least 80% of a complete antitubercular regimen and is considered to be cured by the doctor within 12 months of institution of treatment) | - Date of start of treatment  
- Date of end of treatment  
- For tuberculosis with positive cultures:  
  - Date of positive bacteriological examination  
  - Date of 1st negative bacteriological examination |
| Still under treatment at 12 months | - Planned in initial protocol  
- Stopped treatment for more than 2 months  
- Treatment failure  
- Onset of resistance during treatment  
- Change of treatment |
| Treatment stopped and not renewed | - Diagnosis of tuberculosis ruled out  
- Another reason (intolerance to treatment, etc.) |
| Transfer | State the name of the structure to which the patient was transferred and the country, where applicable.  
- The country of institution of treatment is responsible for making the follow-up report. |
| Death (death before or during treatment, including cases with a post-mortem diagnosis) | - Directly related to the tuberculosis  
- Other causes |
| Patients lost to follow-up | |

Patients who refused treatment from the outset (treatment not begun) are collected on the mandatory reporting form (MRF).
References


All HAS publications are available for download at www.has-sante.fr