

- Title** Laboratory diagnosis of toxoplasmosis in immunocompromised patients HIV-infected patients, haematopoietic stem cell transplant recipients and solid organ transplant recipients
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Aim

This assessment corresponds to the second part of a response to a request from the *Caisse nationale d'assurance maladie des travailleurs salariés* (CNAMTS - National Health Insurance fund for salaried workers), which wishes to update the *Nomenclature des actes de biologie médicale* (NABM - Nomenclature of Procedures in Laboratory Medicine) in relation to procedures for the laboratory diagnosis of toxoplasmosis. This parasitic disease, caused by the protozoan *Toxoplasma gondii*, groups together some very distinct clinical and biological contexts. A first part of the assessment, validated in February 2017, concerned the laboratory diagnosis of acquired toxoplasmosis in immunocompetent subjects (including pregnant women), congenital toxoplasmosis and ocular toxoplasmosis. This second part focuses on diagnostic tests for toxoplasmosis in immunocompromised patients, in particular patients infected with human immunodeficiency virus (HIV), and haematopoietic stem cell transplant (HSCT) or solid organ transplant recipients.

Conclusions

A critical analysis of the literature and consultation of professional organisations have demonstrated that little data is available and that practices differ between healthcare centres. Given this situation and taking into account the rarity, diversity and seriousness of the clinical situations in question, the HAS reaches the following conclusions:

- ▶ Diagnosis of toxoplasmosis in HIV-infected patients
 - Serological screening for toxoplasmosis (testing for anti-Toxoplasma IgG and IgM antibodies) during the initial paraclinical assessment following the discovery of HIV infection enables identification of HIV patients at risk of latent Toxoplasma infection reactivation (patients seropositive for anti-Toxoplasma IgG antibodies). Serological tests should be performed annually if this initial screening test is negative.
 - A diagnosis of cerebral toxoplasmosis in an HIV-infected patient is usually presumptive, based on a set of arguments including a positive serological test for anti-Toxoplasma IgG antibodies. The diagnosis can be confirmed by testing for the

presence of Toxoplasma DNA by gene amplification (Polymerase Chain Reaction [PCR] method) on peripheral blood and/or cerebrospinal fluid (CSF) at the time of initial presentation (sample to be taken before the initiation of empirical treatment) or, in the absence of any clinical response to empirical anti-Toxoplasma treatment, during the first seven to fourteen days of treatment. A negative PCR test for toxoplasmosis does not exclude a diagnosis of active toxoplasmosis.

- Animal inoculation and cell culture techniques, and testing for the local synthesis of antibodies in the CSF are not useful in this context.

▶ Diagnosis of toxoplasmosis in HSCT and solid organ transplant recipients

Serological screening of donors and recipients

- Serological screening for toxoplasmosis (testing for anti-Toxoplasma IgG and IgM antibodies) is a regulatory obligation in France for HSCT or organ donors. The available data does not enable any conclusion to be reached with respect to the need or otherwise to perform additional PCR investigations in the event of detection of anti-Toxoplasma IgM antibodies in the donor's blood.
- In (future) HSCT/organ recipients, serological screening for toxoplasmosis (testing for anti-Toxoplasma IgG and IgM antibodies) makes it possible to identify chronically infected patients at risk of reactivation and, in the case of solid organ transplants, patients not immunised against the risk of transmission of the infection via transplantation of an infected organ.

Diagnosis of active toxoplasmosis in the presence of symptoms

In HSCT/solid organ transplant patients presenting clinical and/or radiological symptoms of active toxoplasmosis:

- testing for the presence of Toxoplasma DNA by gene amplification (PCR) on appropriate biological samples (peripheral blood, BALF, CSF, bone marrow, organ biopsy, other biological fluids, etc.) may make it possible to make a diagnosis, with the type of samples taken guided by the symptoms.

However, a negative PCR test does not exclude a diagnosis of active toxoplasmosis;

- serological tests are of little value;
- animal inoculation and cell culture techniques are not useful in this context.

When the PCR test on peripheral blood is positive in an HSCT/solid organ transplant patient receiving anti-toxoplasmosis treatment, the available data does not permit any conclusion to be reached with respect to the benefit or otherwise of monitoring the efficacy of treatment by PCR testing on blood samples.

Post HSCT/solid organ transplant laboratory monitoring

- Systematic monitoring of *Toxoplasma* by DNA amplification (PCR) on peripheral blood may be an alternative to prophylaxis in HSCT recipients seropositive for toxoplasmosis pre-transplantation and unable to be given effective prophylaxis against toxoplasmosis. However, the available data does not enable methods for the implementation of such monitoring to be proposed. There is no conclusive data to support the use of this type of monitoring in organ transplant patients.
- Monitoring using serological tests may be of potential benefit (not formally demonstrated) in heart transplant patients in a situation of serological discordance (recipient who is seronegative for toxoplasmosis receiving an organ from a chronically infected donor). However, the available data does not enable the frequencies and durations of such monitoring to be specified. There is no conclusive data to support the use of this type of monitoring in HSCT recipients.

► For all the clinical contexts concerned

- The management of toxoplasmosis in these various categories of immunocompromised patients is handled by highly specialised clinical and laboratory teams, generally in a hospital setting. In this context, diagnostic tests for toxoplasmosis should be performed by “expert” toxoplasmosis medical laboratories. An expert laboratory is primarily defined by its ability to perform less widely used techniques or manual techniques, its capacity to handle complex cases, and its inclusion within a think-tank network in collaboration with other expert laboratories and the various clinicians involved in the management of this infection. It should be noted that for non-immunocompromised patients (non-immunocompromised HIV-infected patients, HSCT donors, future HSCT/solid organ transplant recipients), serological tests for toxoplasmosis may be performed outside an expert laboratory in the context of the specific assessments to be performed in these situations.
- Laboratory monitoring (using serological tests and/or PCR) of an immunocompromised patient

must be performed in the same laboratory, using the same techniques, in order to ensure the comparability of results.

- The complex and serious situations in which these immunocompromised patients can find themselves may lead to the performance of certain tests despite the absence of a satisfactory level of evidence of their value, insofar as these tests may contribute to a set of data.

Methods

The method selected is based on a critical analysis of the literature (systematic reviews, meta-analyses, good practice guidelines, technological assessment reports, general reviews), identified by a systematic literature search, together with a request for information from the National Reference Centre for Toxoplasmosis, the French Society for bone marrow transplantation and cell therapy, and the French-speaking Society for transplantation, as stakeholders.

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