# Toxoplasmose : diagnostic et prise en charge

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DU de thérapeutique anti-infectieuse

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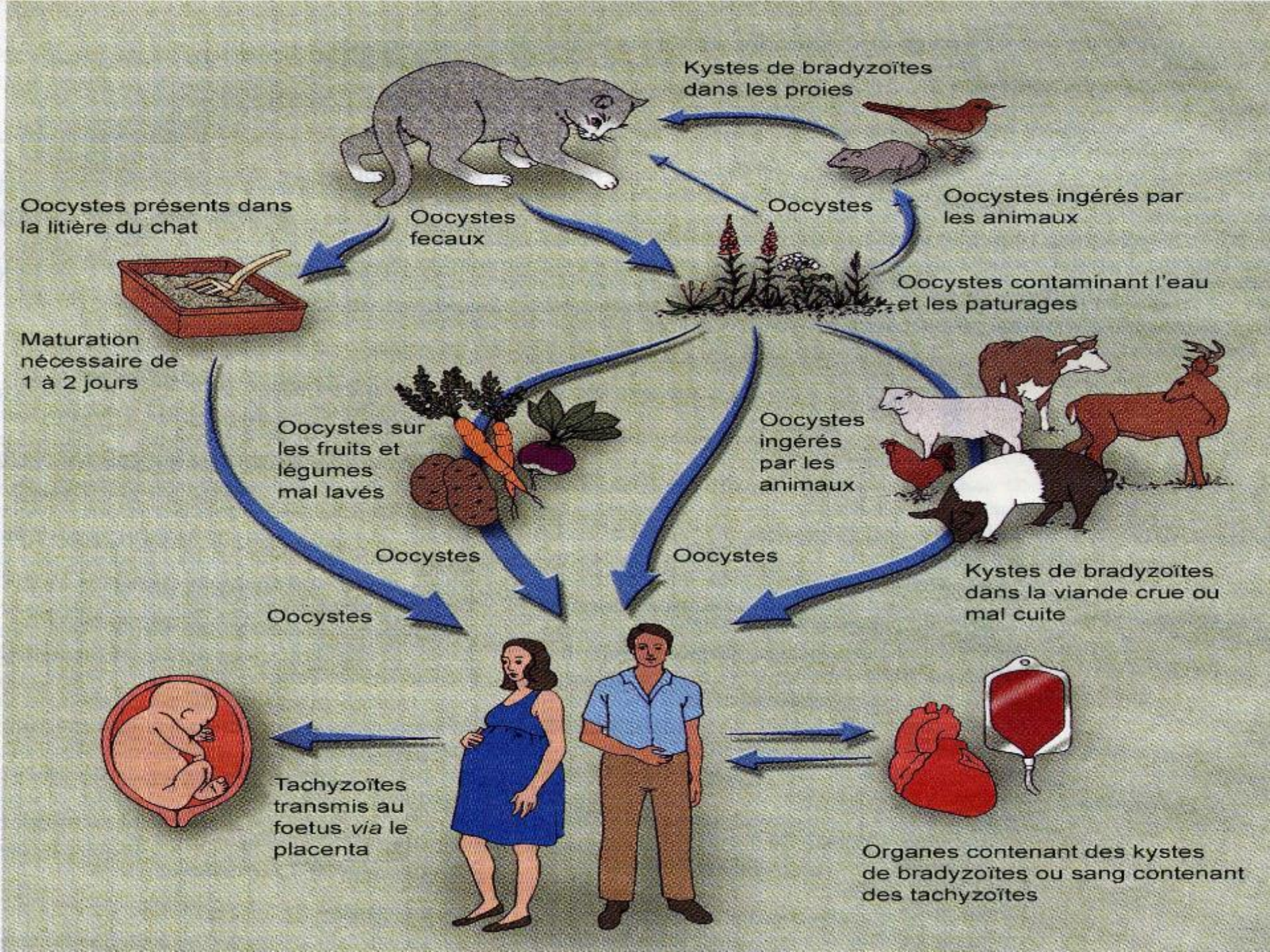
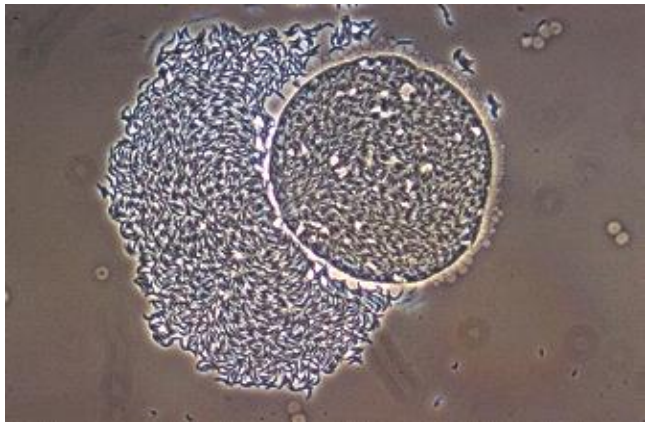
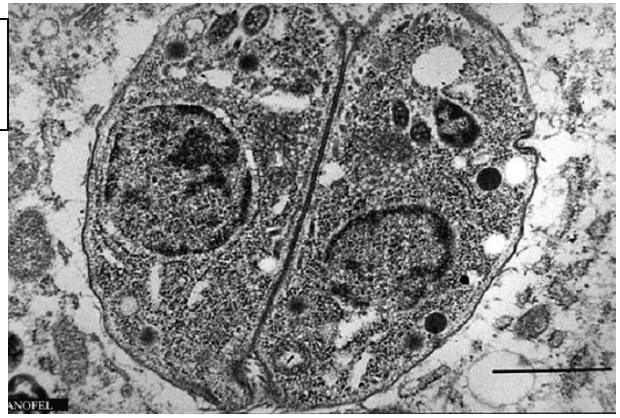

Kystes de bradyzoïtes dans les proies
Oocystes présents dans la litière du chat
Oocystes fecaux
Oocystes
Oocystes ingérés par les animaux
Oocystes contaminant l'eau et les paturages
Maturation nécessaire de 1 à 2 jours
Oocystes sur les fruits et légumes mal lavés
Oocystes ingérés par les animaux
Oocystes
Oocystes
Oocystes
Kystes de bradyzoïtes dans la viande crue ou mal cuite
Tachyzoïtes transmis au foetus *via* le placenta
Organes contenant des kystes de bradyzoïtes ou sang contenant des tachyzoïtes

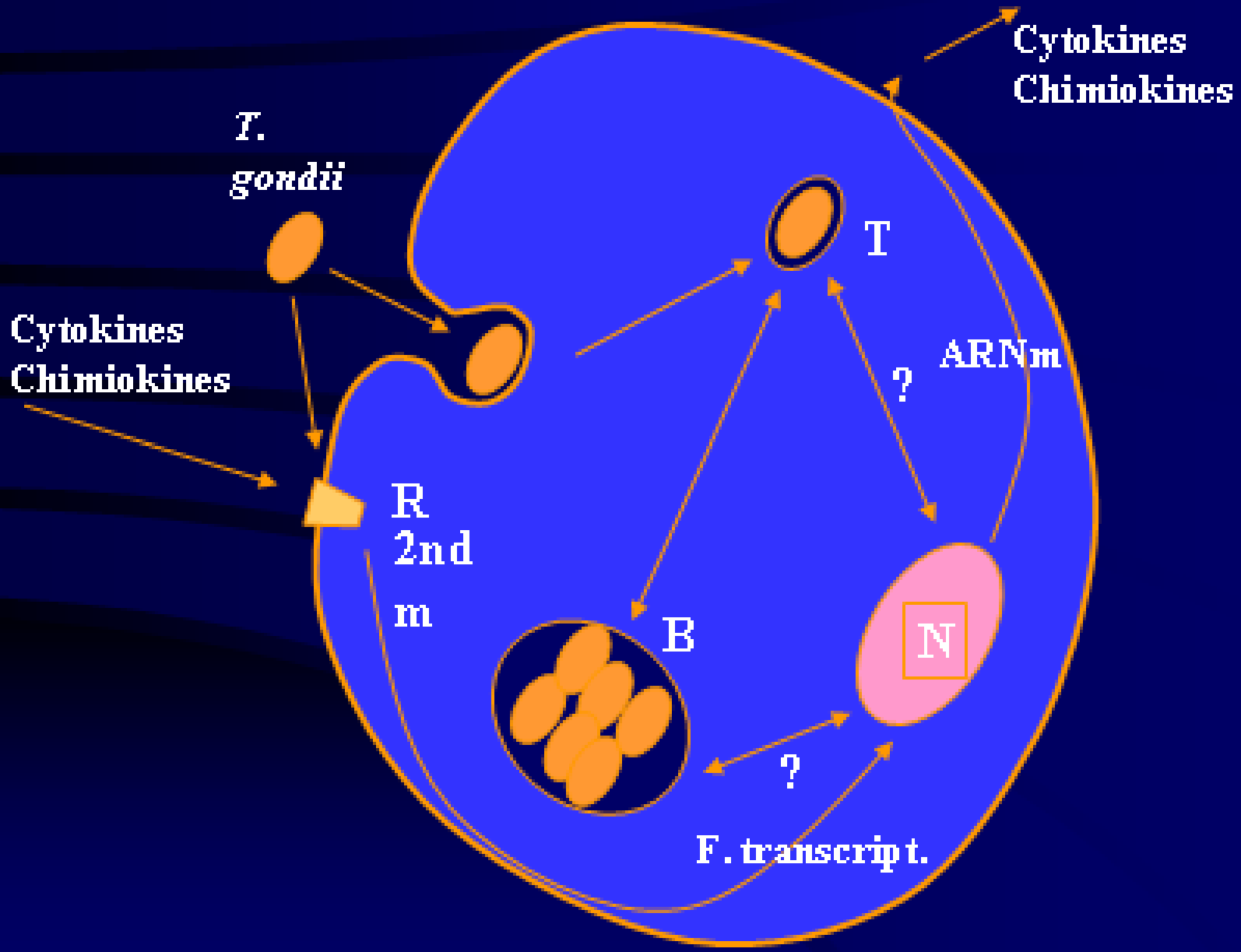


Interconversion




Maubon *et al*, *Trends Parasitol.* 2008

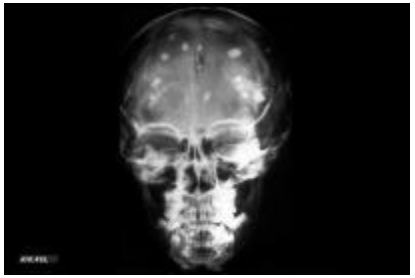
# Interactions *T. gondii*-cellule hôte



# Toxoplasmose congénitale :

# diagnostic et prise en charge

# Introduction



- **toxoplasmose congénitale**

- **importance clinique (France *en l'état actuel de la prise en charge*: 0,5/1000 naissances). 200 à 300 cas/ans sur 6 ans.**

- **épidémiologie (séroprévalence : variable 40 % en France)**

- **diagnostic biologique (séroconversion, diagnostic *in utero*, post natal)**

- **prise en charge selon protocole.**

# Séroconversion - infection maternelle

**Pourquoi ?**

**Objectifs : traiter, prévenir les lésions fœtales**

**Efficacité (Wallon *et al* CID 2013, Garweg *et al* Pathogens 2022)**

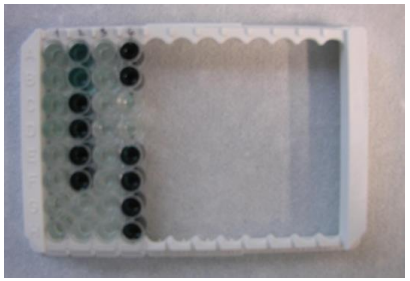
**Cadre légal : différent selon pays (France, Autriche, Suisse +/- …)**

**Dépistage (après la prévention)**

# Séroconversion - infection maternelle

- Dye test

- Blot II



- I.F.I. (Immunofluorescence indirecte)
- Elisa
  - les plus utilisées
  - très nombreuses trousses
  - antigènes, révélations, etc…
  - performances variables selon trousses
- ISAgA
  - précocité
  - sensibilité
  - non automatisée

# Séroconversion - infection maternelle

**Avidité des IgG**

- **évolution de l'Elisa**
- **principe de l'affinité/avidité des anticorps**
- **exclusion d'une infection récente**
- **peu de trousses commerciales disponibles**

# Séroconversion - infection maternelle

## Cinétiques

**cinétiques + avidité**

**= datation de la séroconversion**

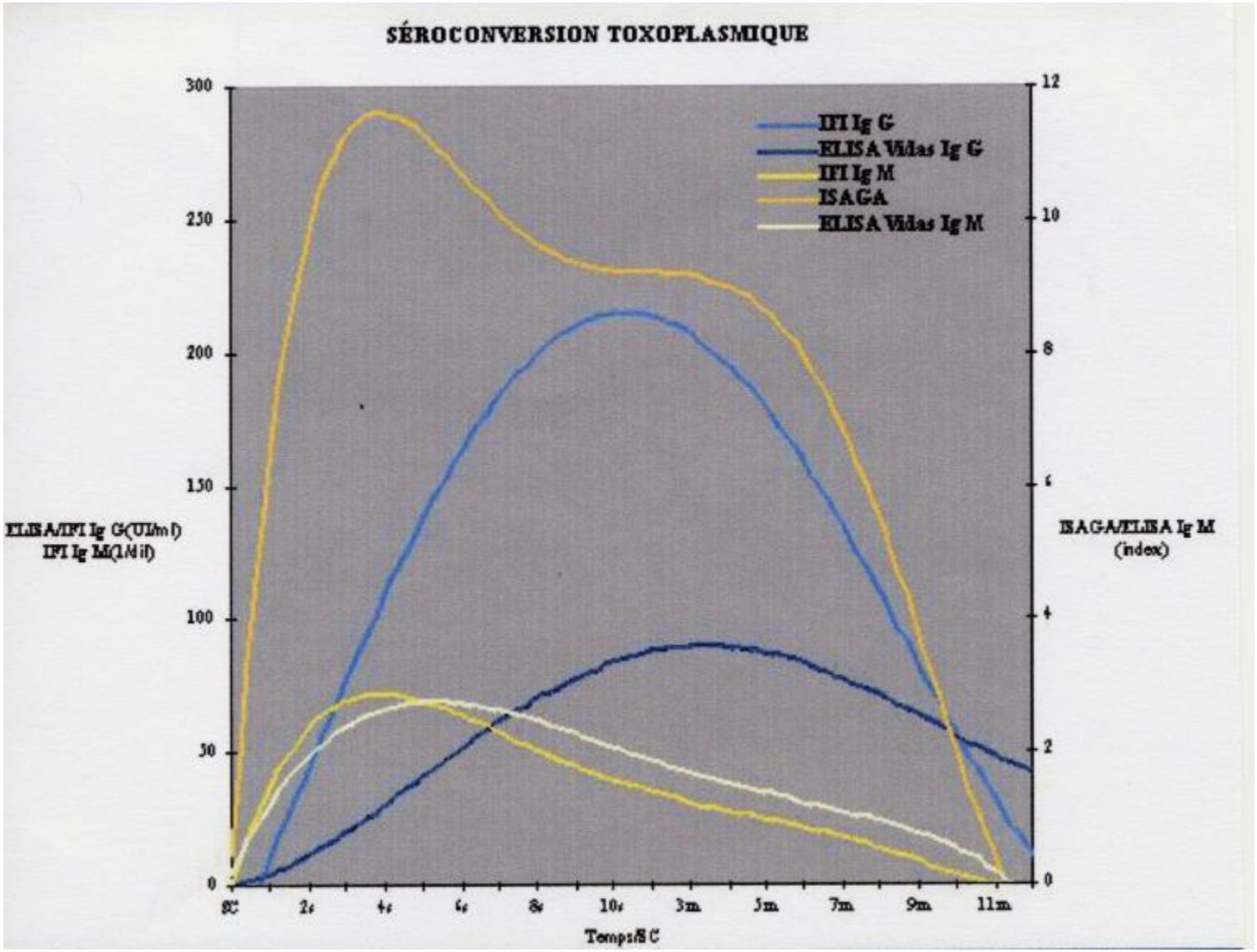
Robert A. & *al*, J. Clin. Microbiol., 2001

**Table 1** Methods and reference centers

| Immunoassay | | | Limits of detection | | | Location of laboratory | Manufacturer | Reference |
|---|---|---|---|---|---|---|---|---|
| No. | Antibody | Principle | Expression | Negative | Positive | | | |
| 1 | IgM | EIA | EIA units | ≤25 | >35 | London, UK | in house | [18] |
| 2 | IgM | MEIA | index | ≤0.5 | ≥0.6 | Ottignies, BEL | commercial[1a] | [19] |
| 3 | IgM | ISAGA | index | 0–5 | ≥9 | London, UK | commercial[1b] | [20] |
| 4 | IgM | ISAGA | index | 0–5 | ≥9 | Vienna, AUS | commercial[1b] | [20] |
| 5 | IgM | ISAGA | dilution | ≤1,024 | ≥2,048 | Stuttgart, GER | in house | [21] |
| 6 | IgM | ISAGA | index | 0–5 | ≥9 | Strasbourg, FR | commercial[1b] | [20] |
| 7 | IgM | IF | dilution | 0–20 | ≥40 | Grenoble, FR | in house | [22] |
| 8 | IgA | EIA | index | 0 | ≥1 | Brussels, BEL | commercial[1c] | [23] |
| 9 | IgA | EIA | index | 0 | ≥2 | Lille, FR | commercial[1c] | [23] |
| 10 | IgA | EIA | index | ≤0 | ≥2 | Swansea, UK | in house | [24] |
| 11 | IgA | ISAGA | index | ≤2 | ≥5 | Toulouse, FR | in house | [25] |
| 12 | IgA | ISAGA | index | 0–5 | ≥9 | Strasbourg, FR | commercial[1d] | |
| 13 | IgA | ISAGA | index | ≤1 | ≥3 | Lausanne, CH | in house | [26] |
| 14 | IgA | WB | + or − | nonreactive | reactive | Würzburg, GER | in house | [27] |
| 15 | IgG | AC/HS | IU/ml | nonacute | acute | Paris 75014, FR | in house | [28] |
| 16 | IgG | avidity | percent | ≥30 | ≤16 | Helsinki, FIN | commercial[1e] | [14] |
| 17 | IgG | avidity | percent | ≥60 | ≤30 | Paris 75674, FR | commercial[1c] | [29] |
| 18 | IgG | avidity | percent | ≥40 | ≤30 | Swansea, UK | in house | [30] |
| 19 | IgG | avidity | percent | ≥30 | ≤15 | Leipzig, GER | in house | |
| 20 | IgE | ISAGA | index | ≤2 | ≥4 | Inverness, UK | in house | [17] |

[a] Abbott
[b] bioMérieux
[c] Sanofi-Pasteur
[d] Clonatech-Biosoft
[e] Labsystems

EIA, enzyme immunoassay, MEIA, microparticle EIA; ISAGA, immunosorbent agglutination assay; IF, immunofluorescence; WB, Western blot; AC/HS, agglutination assay for early IgG; avidity, IgG-avidity EIA; IU, international unit(s); UK, United Kingdom; BEL, Belgium; AUS, Austria; FR, France; CH, Switzerland; FIN, Finland


SÉROCONVERSION TOXOPLASMIQUE
IFI Ig G
ELISA Vidas Ig G
IFI Ig M
ISAGA
ELISA Vidas Ig M
ELISA/IFI Ig G(UI/ml)
IFI Ig M(1/dil)
ISAGA/ELISA Ig M
(index)
300
250
200
150
100
50
0
12
10
8
6
4
2
0
SC
2s
4s
6s
8s
10s
3m
5m
7m
9m
11m
Temps/SC

H Pelloux & *al*, J. Clin. Microbiol., 1997

# Detection of Anti-*Toxoplasma* Immunoglobulin M in Pregnant Women

Liesenfeld et al. (1) recently published a very interesting article on an old but still often embarrassing problem, the detection of anti-*Toxoplasma* immunoglobulin M (IgM) in pregnant women. We completely agree with their conclusions, but we would like to add some more comments.

First, the evaluation of IgM detection with a serology kit is easy when the follow-up of patients allows the collection of consecutive sera which definitely confirm either a seroconversion (with the first serum sample being negative) or a persisting negative serology. However, in routine laboratories, biologists are most often faced with the problem of a first serum sample with IgG and IgM, or IgM alone in a pregnant woman without any previous result. The biologist has to give a first reply to the physician, the definitive conclusion coming from the study of a second serum sample 3 weeks afterward, in countries (such as France) where this is routinely done. Thus it is of great importance for the clinical microbiologist to know perfectly well the performance of the kit he or she uses. This can be ascertained only by carrying out comparative studies with previously described tests, even if none of the techniques is the absolute reference since there is no real "gold standard" for IgM detection, as specified by Liesenfeld et al. (1, 2). A World Health Organization reference serum exists for IgG, but not for IgM (3). That is why the words "sensitivity" and "specificity" must be carefully interpreted in these studies. They are not absolute but are related to the reference technique (which again is not a gold standard) used specifically in each study and clearly defined as such. The real medical sensitivity (together with the earliness of detection) and specificity for the diagnosis of acquired toxoplasmosis can be evaluated only with true seroconversions and consecutive negative sera, respectively.

Second, it is true that the information given to a pregnant woman that she has a positive result in an IgM test for *Toxoplasma* can lead to exaggerated distress, even if successive controls can be performed. We would like to insist on the fact that it is the responsibility of both the physician and the biologist to carefully interpret the results and to discuss together the content of the message to be delivered to the patient. Since no IgM detection kit is absolutely perfect, the clinical microbiologist in a routine laboratory must give not only a reply concerning the test results but also, from a medical point of view, an interpretation concerning the possibility, or not, of infection acquired after the beginning of pregnancy. If this is impossible, he or she should refer the sample to a reference laboratory, which can give more precise information, mainly by comparing the results obtained by different serological methods with different target antigens and antibodies with different kinetics.

This is the only way, to date, to avoid the tragedies that could be induced by false-positive results and/or results indicating persistent (remaining after infection acquired in the distant past) IgM specific for *Toxoplasma gondii*.

## REFERENCES


1. **Liesenfeld, O., C. Press, J. G. Montoya, R. Gill, J. L. Isaac-Renton, K. Hedman, and J. S. Remington.** 1997. False-positive results in immunoglobulin M (IgM) Toxoplasma antibody tests and importance of confirmatory testing: the Platelia Toxo IgM test. J. Clin. Microbiol. **35**:174–178.
2. **Pelloux, H., P. Ciapa, A. Goullier-Fleuret, and P. Ambroise-Thomas.** 1993. Evaluation du système VIDAS pour le diagnostic sérologique de la toxoplasmose. Ann. Biol. Clin. **51**:875–878.
3. **Petithory, J. C., P. Ambroise-Thomas, J. De Loye, H. Pelloux, A. Goullier-Fleuret, M. Milgram, C. Buffard, and J. P. Garin.** 1996. Serodiagnosis of toxoplasmosis: a comparative multicentre study of a series of control sera using various currently available tests and expression of the results in international units. WHO Bull. **74**:291–298.



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***Ed. Note:*** *The authors of the published article declined to respond.*

H. Fricker-Hidalgo & *al*, Diag. Microbiol. Infect. Dis., 2006

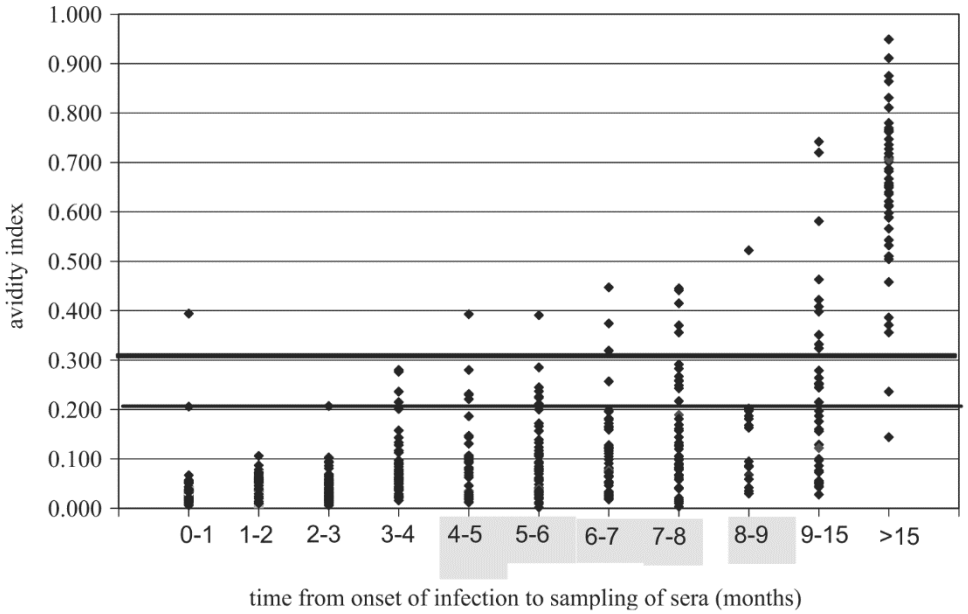



Fig. 2. Avidity index value for 553 sera of pregnant women with recent toxoplasmosis according to the time of infection. Each dot represents 1 serum. The time from the onset of infection to sampling of sera is rounded off to the nearest month. Interpretation of avidity test results: <0.200, low; 0.200 to <0.300, borderline; >0.300, high.

# Séroconversion - infection maternelle

## Difficultés d'interprétation

- inhomogénéité des techniques et des trousses (antigènes, seuils, cinétiques)
- avantage ou inconvénient ? Selon expertise !
- variations individuelles ?
- traitement ?

# Formes cliniques

- **Mort in utero**
- **Méningoencéphalomyélite**
- **Formes dégradées**
- **Choriorétinites**

**Formes inapparentes à la naissance$^{+++}$**

**(choriorétinites)**

# Diagnostic *in utero*

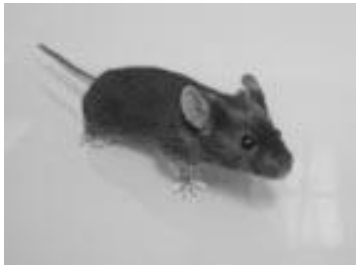
## Indications

- **séroconversion entre 6 et 36 SA.**
- **modification traitement ?**
- **échographie fœtale**

## Prélèvement

- **liquide amniotique**

# Diagnostic *in utero*



**Inoculation à la souris**

- **la plus ancienne**
- **isoler les souches**
- **animalerie (difficulté…)**
- **peu de laboratoires**

# Diagnostic *in utero*

## PCR qualitative

- **plusieurs séquences cibles (P30, TGR1E, B1, Rep 529)**
- **hétérogénéité des techniques**
- **« in house »**
- **a permis de s'affranchir de la cordocentèse**

# Diagnostic *in utero*

## PCR quantitative

- « standardisation » technique ?

- valeur clinique de la quantification ?

Pelloux H. & *al*, FEMS Microbiol. Lett., 1998

## Summary of results for the detection of *Toxoplasma gondii* in artificial samples using the polymerase chain reaction

| Laboratory | Number of Toxoplasma gondii tachyzoïtes in 1 ml amniotic fluid | | | | | | | | Number of negative control samples found positive among4 |
|---|---|---|---|---|---|---|---|---|---|
| | 1 | 1 | 10 | 10 | 100 | 100 | 1000 | 1000 | |
| J | + | + | + | + | + | + | + | + | 0 |
| N | + | + | + | + | + | + | + | + | 0 |
| C | - | + | + | + | + | + | ++ | ++ | 0 |
| F | - | + | + | ++ | +++ | ++++ | +++ | ++++ | 0 |
| O | - | + | + | + | + | + | ++ | ++ | 0 |
| L | ± | ± | + | + | ++ | ++ | +++ | +++ | 0 |
| M | - | - | + | + | + | + | + | + | 0 |
| K | - | - | - | ± | + | + | + | + | 0 |
| D | - | - | - | - | + | + | + | + | 0 |
| B | - | - | - | - | - | - | - | - | 0 |
| G | - | - | - | - | - | - | - | - | 0 |
| E | - | + | - | - | + | + | ++ | ++ | 1 |
| H | - | + | - | + | + | + | + | + | 1 |
| I | - | + | - | - | + | + | + | + | 1 |
| A | - | - | + | + | + | + | - | - | 4 |
| Total number of positive samples | 12/30 (40 %) | | 18/30 (60 %) | | 26/30 (86 %) | | 24/30 (80 %) | | 7/60 (11,6 %) |

S. Romand & *al*, Am. J. Obst. Gyn., 2004

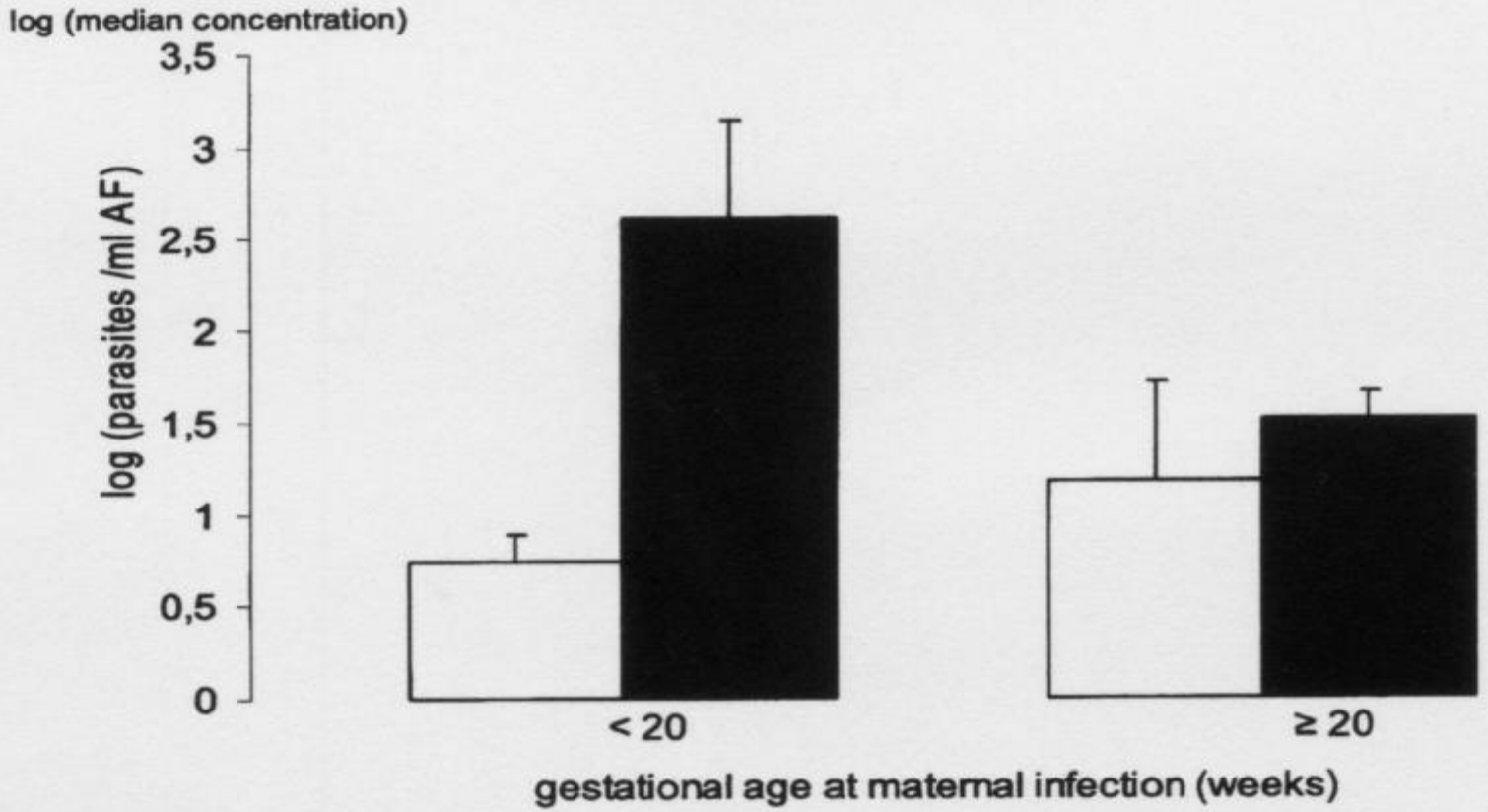



**Figure 2** Comparison of median (interquartile range) parasite concentrations in AF between cases with subclinical infection (*unshaded bars*) and cases with infectious sequelae (*shaded bars*) for maternal infections acquired before or after 20 weeks' gestation. Clinical status was recorded either at birth or after fetal death (fetopathologic examination).

# Diagnostic *in utero*

**Valeur du diagnostic *in utero***

- **sensibilité/spécificité de la PCR (qualitative et quantitative)**
- **apport de la quantification ?**

# Diagnostic *in utero*

**Toutes techniques et prélèvements confondus**

**- sensibilité du diagnostic anténatal entre 90 et 100 %**

**- spécificité 100 %**

# Diagnostic néonatal et postnatal

**Pourquoi ? Indications**

- **enfant né d'une mère ayant présenté une infection toxoplasmique pendant la grossesse**
- **diagnostic *in utero* ou non**
- **traitement ?**
- **« gold standard » : sérologie à un an**

# Diagnostic néonatal et postnatal

## Placenta

- intéressant si absence de diagnostic ante-natal (Robert-Gangneux *et al*, *Trends Parasitol.* 2011)

- souris, PCR

- sensibilité, spécificité

# Suivi du nouveau né et de l'enfant

**Sérologies « classiques »**

- **IgG, IgM, IgA**
- **IFI, ELISA, ISAgA**
- **cinétique**
- **persistance ou disparition des IgG**

# Suivi du nouveau né et de l'enfant

## Western Blot

- profils comparés mère/enfant

-permet de mettre en évidence les anticorps néo-synthétisés par le nouveau-né

# Suivi du nouveau né et de l'enfant

## Protocole de suivi

naissance (J +5), 1 mois, puis tous les 2 mois jusqu'à 6 mois

puis suivi sérologique jusqu'à un an, sauf si négativation des IgG

J. M. Pinon & *al*, J. Clin. Microbiol., 2001

TABLE 1. Sensitivities and specificities of individual and CIP methods for diagnosis of CT[a]

| Parameter and method[b] | Performance at age: | | | Cumulative performance, 0–12 mo |
|---|---|---|---|---|
| | 0–10 days | 0.5–1.5 mo | 2–12 mo | |
| Sensitivity | | | | |
| Individual methods | | | | |
| ISAGA-M | 27/40 (67.5)[c] | 17/27 (62.9) | 12/42 (28.6) | 43/53 (81.1) |
| ISAGA-A | 29/40 (72.5) | 18/27 (66.6) | 21/42 (50) | 44/53 (83) |
| EIA-M | 26/42 (61.9) | 17/29 (58.6) | 6/42 (14.2) | 35/54 (64.8) |
| EIA-A | 30/42 (71.4) | 17/30 (56.6) | 16/42 (38) | 45/54 (83.3) |
| ELIFA-G | 26/38 (64.2 [5[d]]) | 22/30 (73.3) | 38/43 (88.3) | 48/54 (88.8) |
| ELIFA-M | 7/42 (16.6) | 6/29 (20.6) | 6/40 (15) | 12/54 (22.2) |
| IB-G | 16/40 (40 [2]) | 19/30 (63.3) | 29/43 (67.4) | 36/55 (65.4) |
| IB-M | 21/37 (56.7 [6]) | 20/29 (68.9) | 23/41 (56) | 37/54 (68.5) |
| Combined methods | | | | |
| ISAGA-M + ISAGA-A | 30/39 (76.9) | 20/27 (74) | 24/42 (57.1) | 49/53 (92.4) |
| EIA-M + EIA-A | 34/42 (80.9) | 23/29 (79.3) | 18/42 (42.8) | 47/54 (87) |
| ELIFA-G + ELIFA-M | 28/38 (73) | 22/29 (75.8) | 35/40 (87.5) | 48/54 (88.8) |
| IB G + IB M | 24/37 (64.8) | 22/29 (75.8) | 30/41 (73.1) | 42/54 (77.7) |
| ELIFA-G + ELIFA-M + EIA-M + EIA-A | 35/38 (92.1) | 26/27 (96.2) | 37/40 (92.5) | 49/51 (96) |
| ELIFA-G + ELIFA-M + ISAGA-M + ISAGA-A | 32/36 (88.8) | 24/25 (96) | 36/40 (90) | 49/50 (98) |
| IB-G + IB-M + EIA-M + EIA-A | 30/37 (81) | 26/29 (89.6) | 32/41 (78) | 46/51 (90.1) |
| IB-G + IB-M + ISAGA-M + ISAGA-A | 28/32 (87.5) | 24/27 (88.8) | 33/41 (80.4) | 47/50 (94) |
| Specificity | | | | |
| Individual methods | | | | |
| ISAGA-M | 21/27 (77.7) | 27/28 (96.4) | 34/34 (100) | 43/50 (86) |
| ISAGA-A | 21/27 (77.7) | 29/29 (100) | 35/35 (100) | 44/50 (88) |
| EIA-M | 24/27 (88.8) | 32/32 (100) | 37/37 (100) | 47/50 (94) |
| EIA-A | 23/27 (85.1) | 31/32 (96.8) | 37/37 (100) | 43/50 (86) |
| ELIFA-G | 17/17 (100 [10]) | 31/31 (100 [1]) | 37/37 (100) | 50/50 (100) |
| ELIFA-M | 27/27 (100) | 31/31 (100) | 33/33 (100) | 50/50 (100) |
| IB-G | 26/27 (96.2) | 31/32 (96.8) | 36/36 (100) | 48/50 (96) |
| IB-M | 27/27 (100) | 31/31 (100 [1]) | 34/35 (97.1) | 49/50 (98) |
| Combined methods | | | | |
| ISAGA-M + ISAGA-A | 20/27 (7) | 27/28 (96.4) | 34/34 (100) | 46/50 (92) |
| EIA-M + EIA-A | 21/27 (77.7) | 31/32 (96.8) | 37/37 (100) | 41/50 (82) |
| ELIFA-G + ELIFA-M | 17/17 (100 [10]) | 31/31 (100 [1]) | 33/33 (100) | 50/50 (100) |
| IB-G + IB-M | 26/27 (96.2) | 30/31 (96.7) | 34/35 (97.1) | 48/50 (96) |
| ELIFA-G + ELIFA-M + EIA-M + EIA-A | 20/27 (74) | 27/28 (96.4) | 34/34 (100) | 42/50 (84) |
| ELIFA-G + ELIFA-M + ISAGA-M + ISAGA-A | 21/27 (77.7) | 30/31 (96.7) | 37/37 (100) | 41/50 (82) |
| IB-G + IB-M + EIA-M + EIA-A | 19/27 (70.3) | 26/28 (92.8) | 33/34 (97) | 40/50 (80) |
| IB-G + IB-M + ISAGA-M + ISAGA-A | 22/27 (81.4) | 29/31 (93.5) | 34/35 (97.1) | 38/50 (76) |

[a] Sera from 55 babies with CT and 50 case-controls were separated according to the sampling date.
[b] ISAGA-M, ISAGA for IgM detection; ISAGA-A, ISAGA for IgA detection; EIA-M, IgM immunocapture-based EIA; EIA-A, IgA immunocapture-based EIA; ELIFA-G, ELIFA for IgG detection; ELIFA-M, ELIFA for IgM detection; IB-G, IB assay for IgG detection; IB-M, IB assay for IgM detection.
[c] Data represent number of positive serum samples/number of serum samples tested (percent).
[d] Data in brackets are the number of samples with uninterpretable ELIFA or IB assay results and are excluded from the final calculation.

D. Tissot Dupont & *al*, Eur. J. Clin. Microbiol. Infect. Dis., 2003

**Table 1** Sensitivity and specificity of Western blot and IgM immunosorbent agglutination assay (IgM-ISAGA) used to detect *Toxoplasma gondii* at birth and within the first 3 months of life

| Test method | Sensitivity | Specificity |
|---|---|---|
| At birth[a] | | |
| Western blot (IgG, IgM, IgA) | 65.2% (15/23) | 96.1% (98/102) |
| IgM-ISAGA | 60.9% (14/23) | 93.1% (95/102) |
| Within 3 months[b] | | |
| Western blot (IgG, IgM, IgA) | 82.6% (19/23) | 96.6% (87/90) |
| IgM-ISAGA | 69.6% (16/23) | 100% (92/92) |
| At birth and within 3 months | | |
| Western blot (IgG, IgM, IgA) | 86.9% (20/23) | 96.1% (99/103) |
| IgM-ISAGA | 69.6% (16/23) | 92.2% (95/103) |

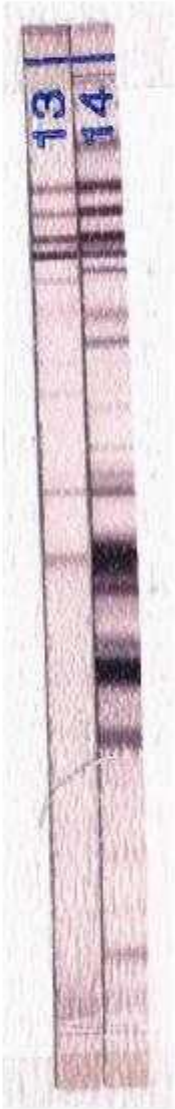
[a] Positive test result obtained at least from cord blood and neonate serum collected at day 0 or day 5

[b] Positive test result obtained at least once within the first 3 months of life (birth excluded)

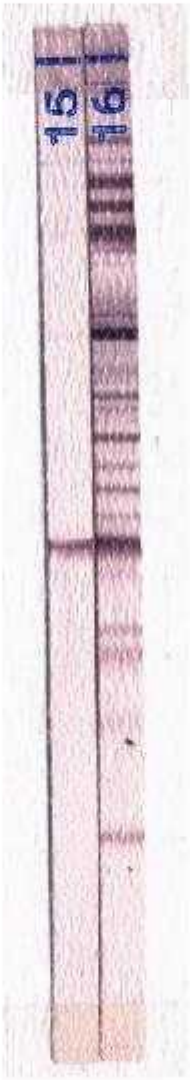
**13 et 15 : bb J 1**

**14 et 16 : bb 1 mois**

**IgG**




**IgM**



# Prise en charge pratique

**Femme enceinte positive : pas de suivi**

**Femme enceinte négative :**

**- sérologie mensuelle**

**- règles hygiéno-diététiques**

**Si séroconversion : la dater**

**- périconceptionnelle à 6 SA :**

**écho, Spiramycine 9 MU/J**

**- 6 SA à 36 SA :**

**écho, Spira, diagnostic antenatal**

**suivant résultat : - Spiramycine**

**- Pyrimethamine (50mg/j) – Sulfadiazine (3g/j)**

**- Sulfadoxine (2cp/s)**

**discussion IMG**

**Après 36 SA**

**- écho, Pyr-Sulfa, amniocentèse, déclenchement ?**

**A la naissance :**

- **Bilan clinique et neuro (FO, ETF…)**
- **Biologie (sérologie + placenta)**
- **Pas d'arguments : pas de traitement**
- **Si toxo congénitale : traitement Pyr-Sulfadox 1 an (1/2 cp pour 10 kg tous les 10 jours)**
- **Gold standard : sérologie à 1 an**

# Choriorétinite toxoplasmique

- **Forme clinique la plus fréquente**

- **Diagnostic :**

  . **Fond d'œil**

  . **Coefficient C (Desmonts), WB**

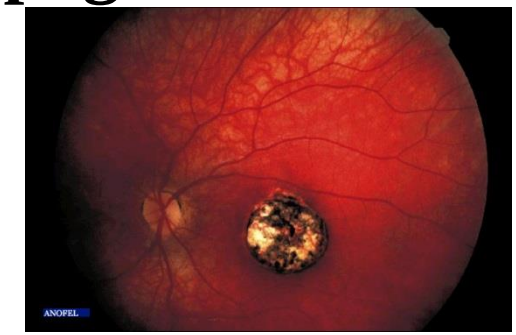
  . **PCR**

- **Traitement : Pyr – Sulfadiazine, Triméthoprime-Sulfaméthoxazole, Pyr-Azithro**

# Perspectives

- typage des souches et serotypage ?

- charge parasitaire ?




- nouveaux traitements ?

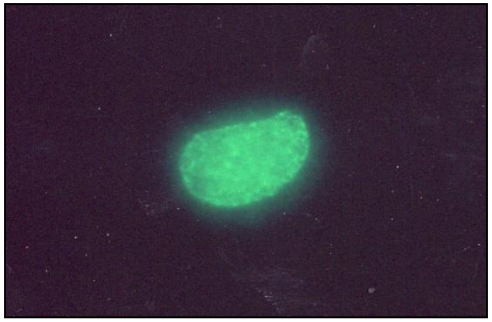
- groupes de travail (sero, biomol) CNR toxo

- HAS 2009, 2017… prise en charge NABM ?

- PHRC Toscane et Toxogest (Mandelbrot et *al* 2018, 2020)…

Nouvelles données ?

# Toxoplasmose chez le patient immunodéprimé
# Diagnostic et prise en charge



# Introduction

- **Tachyzoites/bradyzoites - kystes**
- **réactivations**
- **importance de la maladie sous jacente**
  - **SIDA**
  - **autres patients ID : greffe, hématologie, …**

# Introduction

**Diagnostic :**

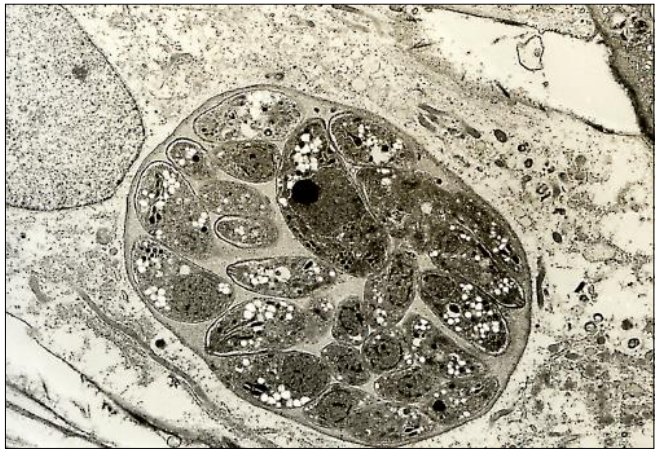
- **clinique**
- **imagerie**
- **biologie :**
  - **sérologie**
  - **P.C.R.**
  - **(antigènes ?)**

# SIDA

**Épidémiologie :**

- **épidémiologie du SIDA**
- **épidémiologie de la toxoplasmose**
- **traitement de l'infection par le VIH**
- **prévention des réactivations toxoplasmiques**

# SIDA



**Principalement :**

- **toxoplasmose cérébrale**
- **avant/après HAART (1995/96)**
- **interruption de la prophylaxie primaire**

**(Miro *et al*, CID 2006)**

# SIDA

**Abgrall *et al* CID 2001**

**19,598 AIDS patients 1992-95 (CD4≤ 200 x $10^6$ cells/l)**

**17,016 AIDS patients 1996-98**

- **Incidence de la TC en France :**

  **3.9 cas/100 personne-année 1992-95**

  **1.0 cas/100 personne-année 1996-98**

- **Si HAART et CD4 > 200 x $10^6$ cells/l**

  **0.1 case/100 personne-année (même si arrêt du cotrimoxazole**)

**Jones & Roberts, CID 2012: évolution identique USA (rupture en 1995)**

# SIDA

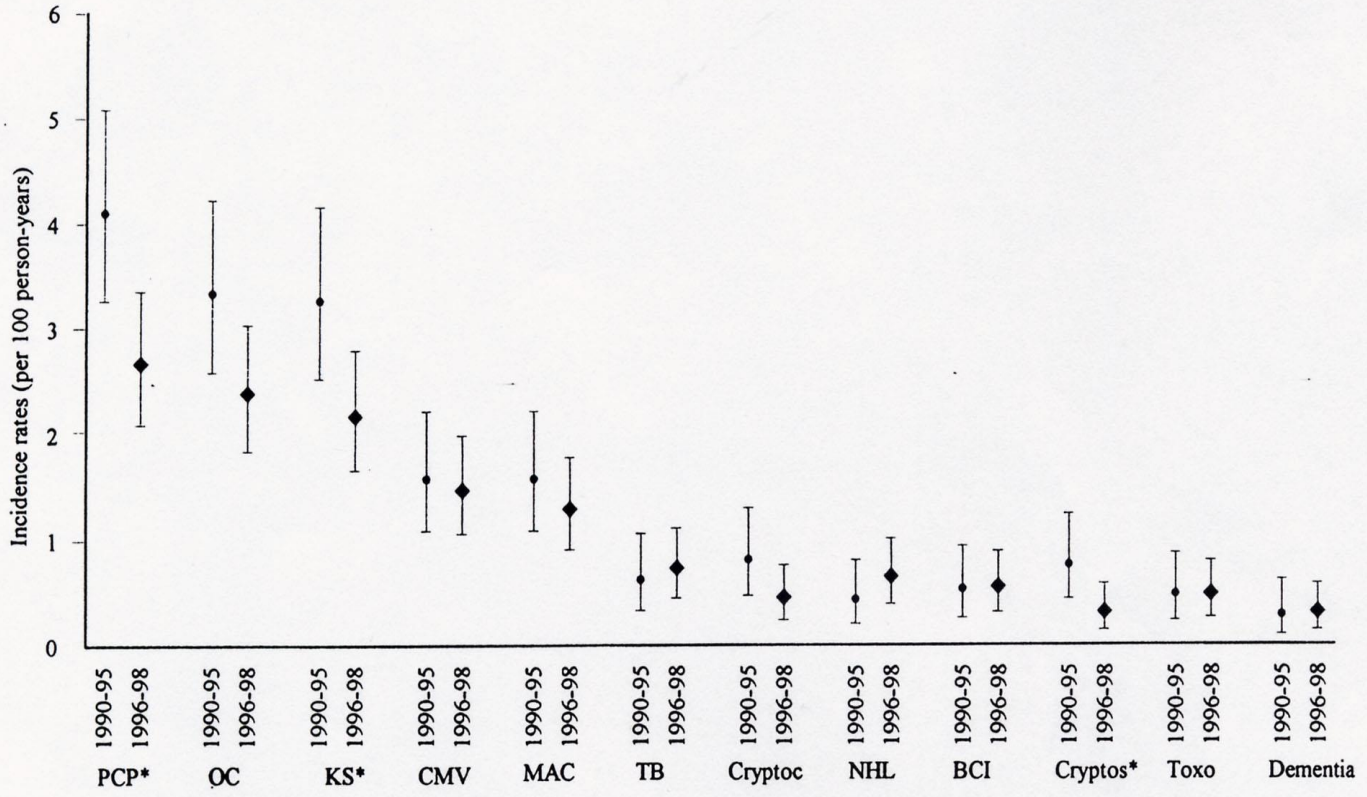
***First AIDS-defining event in respective region. Conditions with at least 40 cases presented***

| AIDS defining event* | All centres ($n = 6546$) | % | North ($n = 2510$) | % | Central ($n = 1932$) | % | Southeast ($n = 1095$) | % | Southwest ($n = 1009$) | % | *P*-value |
|---|---|---|---|---|---|---|---|---|---|---|---|
| PCP | 2517 | 38·5 | 1250 | 49·8 | 688 | 35·6 | 336 | 30·7 | 243 | 24·1 | < 0·001 |
| Kaposi's sarcoma | 1394 | 21·3 | 680 | 27·1 | 488 | 25·3 | 113 | 10·3 | 113 | 11·2 | < 0·001 |
| Oesophageal candidiasis | 1212 | 18·5 | 395 | 15·7 | 330 | 17·1 | 289 | 26·4 | 198 | 19·6 | < 0·001 |
| Extrapulmonary tuberculosis | 571 | 8·7 | 50 | 2·0 | 115 | 6·0 | 51 | 4·7 | 355 | 35·2 | < 0·001 |
| Toxoplasmosis | 512 | 7·8 | 109 | 4·3 | 216 | 11·2 | 96 | 8·8 | 91 | 9·0 | < 0·001 |
| HIV wasting | 328 | 5·0 | 100 | 4·0 | 62 | 3·2 | 79 | 7·2 | 87 | 8·6 | < 0·001 |
| AIDS dementia complex | 295 | 4·5 | | 3·2 | 110 | 5·7 | 96 | 8·7 | 9 | 0·9 | < 0·001 |
| Malignant lymphoma | 228 | 3·5 | 89 | 3·6 | 57 | 3·0 | 49 | 4·5 | 33 | 3·3 | 0·17 |
| Cryptosporidosis | 216 | 3·3 | 85 | 3·4 | 79 | 4·1 | 16 | 1·5 | 36 | 3·6 | < 0·001 |
| Herpes simplex ulcer | 199 | 3·0 | 44 | 1·8 | 111 | 5·8 | 26 | 2·4 | 18 | 1·8 | < 0·001 |
| Cryptococcosis | 158 | 4 | 41 | 1·6 | 33 | 1·7 | 54 | 4·9 | 30 | 3·0 | < 0·001 |
| CMV retinitis | 154 | 2·5 | 57 | 2·3 | 28 | 1·5 | 44 | 4·0 | 25 | 2·5 | < 0·001 |
| *Mycobacterium avium* complex | 104 | 1·6 | 47 | 1·9 | 48 | 2·5 | 5 | 0·5 | 4 | 0·4 | < 0·001 |
| Salmonellosis | 70 | 1·1 | 12 | 0·5 | 22 | 1·1 | 13 | 1·2 | 23 | 2·3 | < 0·001 |
| PML | 47 | 0·7 | 14 | 0·6 | 10 | 0·5 | 17 | 1·6 | 6 | 0·6 | 0·005 |

* PCP, *Pneumocystis carinii* pneumonia; PML, progressive multifocal leucoencephalopathy.

Blaxhult *et al*, Epidemiol. Infect. 2000

# SIDA

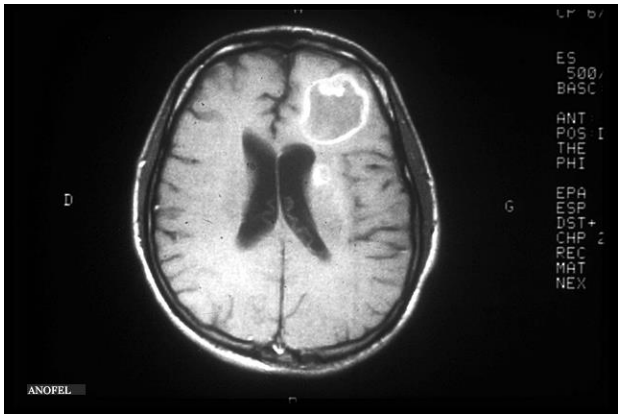



PCP=Pneumocystis carinii pneumonia; OC=oesophageal candidiasis; KS=Kaposi's sarcoma; CMV= cytomegalovirus disease;
MAC= mycobacterium avium complex; TB=tuberculosis; Crytoc=cryptococcosis; NHL=non-Hodgkins lymphoma;
BCI= recurrent bacterial chest infections; Cryptos=cryptosporidiosis; Toxo=cerebral toxoplasmosis; Dementia=dementia
* p-value<0.05

**Figure 1.** Incidence rates and 95% confidence intervals for the twelve most frequent AIDS-defining illnesses for the two periods 1990–1995 (●) and 1996–1998 (♦).

Ives *et al* J. Infect. 2001

# SIDA




## Diagnostic

- clinique: toxo cérébrale (lésions focales, fièvre, céphalées, désorientation, aphasie, ataxie, comitialité…)
- imagerie (abcès cérébral)
- évolution sous traitement
- biologie valeur ?
- Toxo oculaire, toxo pulmonaire

# SIDA

- **Sérologie**

**détermine le statut du patient**

**→ risque de réactivation ou non ?**

**→ valeur prédictive des titres d'anticorps ?**

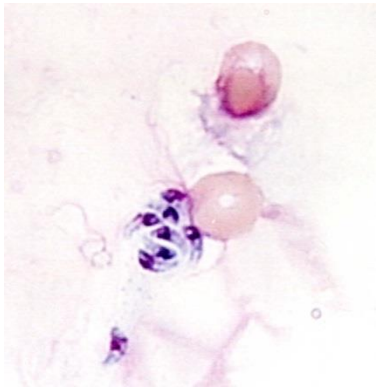
**(Belanger *et al* CID 1999)**

**→ western blot : prédiction de la réactivation ?**

**(Pelloux *et al* AIDS 1992, Leport *et al*, Clin Diag Lab Immunol 2001)**

# SIDA

- **Détection directe de *Toxoplasma* (PCR ++)**
  - **LCR : faible sensibilité**
    **spécificité élevée**



  - **sang périphérique**
    **pas d'intérêt en pratique**
    **(Pelloux *et al* AIDS 1997, Ajzenberg *et al* PloS NTD 2016 )**

  - **problème publis Brésil ??**

  - **(biopsies cérébrales : si traitement inefficace)**

**SIDA**

**Traitement curatif 6 semaines:**

**Pyriméthamine – Sulfadiazine**

**(100 mg 1 jour puis 1mg/kg/j, 25mg/kg/j ac folinique et 100mg/kg/j max 6g/j)**

**Pyriméthamine – Clindamycine (2,4g/j)**

**Prophylaxie :**

**- primaire : Trimethoprim – Sulfamethoxazole. Alternative Dapsone + Pyriméthamine**

**- secondaire : Pyr-Sulfa (25mg/j et 2g/j)**

**Arrêt de la prophylaxie (CD4 > 200 $mm^3$ 6 mois pour secondaire, 3 mois pour primaire)**

# SIDA

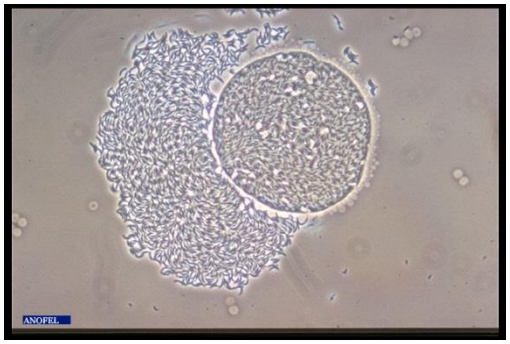
**Toxicité:**

**Hypersensibilité (20-40%): éruption, rash, Stevens Johnson, Lyell, choc**

**Hématologique (10-30%): leucopénie, agranuloytose**

**Rénale (5-10%): cristallurie, anurie**

# SIDA




**Conclusion :**

**- épidémiologie modifiée par les HAART (ART) (Low *et al* CID 2016)**

**- diagnostic : principalement clinique**

**- la sérologie indique la possibilité de réactivation**

# Non-SIDA

- **Deux mécanismes :**
  - **réactivation (≈ SIDA)**
  - **transmission par le greffon**

    **(mismatch donneur ⊕ /receveur ⊖)**

# Non-SIDA

- **Hétérogénéité des tableaux cliniques (≠ SIDA)**

  **- fièvre, organes différents atteints,**
  **toxo disséminée…**

- **Les signes cliniques sont moins spécifiques, donc l'importance des données biologiques est plus grande…**

# Non-SIDA

- **Épidémiologie**

**pas de données épidémiologiques à large échelle (Robert-Gangneux et *al* Emerging Infect Dis 2018)**

**cas isolés ou petites séries (Schmidt *et al* CID 2013)**

**transplantation de coeur, foie, rein, moelle osseuse...**

**importance prophylaxie AHSCT (Conrad *et al* CMI 2016)**

# Non-SIDA

**Un exemple : épidémiologie de la toxoplasmose dans la transplantation cardiaque**

**Montoya *et al*, CID 2001**

- **620 transplantations cardiaques consécutives (15 years)**
- **32 D+/R-**
- **16 recevaient une prophylaxie : pas de toxoplasmose**
- **16 ne recevant pas de prophylaxie : 4 toxoplasmoses, tous décédés**
- **98 R+ : pas de réactivations**

# Non-SIDA

## Greffe de moelle osseuse

**Martino *et al* CID, 2000**

- **15 centres Européens (4 années> 10 000 transplantations)**
- **41 cas de toxoplasmose**
- **94 % étaient des réactivations**
- **63 % sont décédés de toxoplasmose**

# Non-SIDA

- **Diagnostic : valeur des techniques biologiques**

  **- sérologie : parfois impossible à interpréter chez les patients très immunodéprimés (hématologie)**

  **(Fricker-Hidalgo *et al* 2009)**

  **- évaluation du risque de transmission**

  **mismatch D ⊕ /R ⊖ ? (Fernandez-Sabé *et al* 2011)**

  **→ prophylaxie pour le receveur**

# Non-SIDA

- **Détection du parasite +++**

  **PCR ++ (RT-PCR : suivi de la charge parasitaire pendant le traitement ?)**

  **(Patrat-Delon *et al* 2010, Mulanovich *et al* 2011, Caner *et al* 2012)**

  **Suivi des patients à risque ? (Fricker-Hidalgo *et al* 2009, Meers *et al* 2010, Cavattoni *et al* 2010, Busemann *et al* 2012; Robert-Gangneux *et al* 2015)**

- **biopsies, B.A.L., …, preuve de l'infection d'un organe (poumon, coeur…)**

# Non-SIDA

- **Suivi de la parasitémie en cas de greffe de moelle osseuse (Martino *et al*, CID 2005)**
- **106 receveurs séro ⊕ pendant 6 mois après GMO**
- **Infection toxoplasmique (PCR ⊕) : 16 %**
  **(dont incidence de toxoplasmose maladie : 38 %)**
- **Toxoplasmose disséminée : 6 %**
- **Aucune toxoplasmose disséminée chez les patients sans parasitémie détectée par PCR.**

# Diagnosis of Toxoplasmosis after Allogeneic Stem Cell Transplantation: Results of DNA Detection and Serological Techniques

**Hélène Fricker-Hidalgo,[1] Claude-Eric Bulabois,[2] Marie-Pierre Brenier-Pinchart,[1] Rebecca Hamidfar,[3] Frédéric Garban,[2] Jean-Paul Brion,[4] Jean-François Timsit,[3] Jean-Yves Cahn,[2] and Hervé Pelloux[1]**

[1]Parasitologie-Mycologie, Pôle Biologie, [2]Hématologie, Pôle Cancérologie, and [3]Réanimation Médicale and [4]Maladie Infectieuse, Pôle Médecine Aigüe et Communautaire, Centre Hospitalier Universitaire, Grenoble, France

***Background.*** The biological diagnosis of toxoplasmosis after allogeneic hematopoietic stem cell transplantation (HSCT) is based on the detection of *Toxoplasma gondii* DNA in blood specimens or other samples. Serological testing is used mainly to define the immunity status of the patient before HSCT. The aim of our study was to examine the performance of polymerase chain reaction (PCR) and serological techniques in the diagnosis of toxoplasmosis after HSCT.

***Methods.*** Seventy patients underwent allogeneic HSCT from September 2004 through September 2006. DNA was detected by PCR, and immunoglobulin G and immunoglobulin M were detected by enzyme-linked immunosorbent assay.

***Results.*** The results of immunoglobulin G detection before allogeneic HSCT were positive in 40 (57.1%) of the patients and negative in 30 (42.9%). After HSCT, 57 patients (81.4%) had test results that were negative for immunoglobulin M and had negative results of DNA detection, without toxoplasmosis infection. Four patients (5.7%) had at least 4 samples with positive PCR results and/or test results positive for immunoglobulin M against *T. gondii;* toxoplasmosis was then confirmed by clinical symptoms. Nine patients (12.9%) with positive PCR results and 1 or 2 samples with test results negative for immunoglobulin M were considered to have asymptomatic *T. gondii* infection. Reactivation of latent infection was the cause of toxoplasmosis in 3 of the 4 patients, and toxoplasmosis occurred as a primary infection in 1 patient. The detection of specific anti–*T. gondii* immunoglobulin M was the only biological evidence of toxoplasmosis in 2 patients, and samples were positive for immunoglobulin M before PCR was performed in 1 patient.

***Conclusions.*** Thus, after HSCT, all patients were at risk for toxoplasmosis; all patients who receive HSCTs should be followed up with biological testing that combines PCR and serological techniques.

Non-SIDA

**Toxo infection/ toxo maladie**

**-Martino *et al* 2005 (TI 16%, TD 6%) (prophylaxie primaire si possible)**

**-Adurthi *et al* 2008 (TI 13%, TD 0.6%) (pas de prophylaxie systématique)**

**-Fricker-Hidalgo *et al* 2009 (TI 12.8%, TD 5.7%) (prophylaxie primaire si possible)**

**-Meers *et al* 2010 (TI 5.8%, TD 3%) (pas de prophylaxie systématique)**

# Non-SIDA

- **Détection de la parasitémie**
  **- affirme le risque d'une toxoplasmose disséminée**
  **- suivi pendant le traitement**

- **quelle interprétation si négative ?**

## Schéma thérapeutique et prophylactique

- **Pyriméthamine – Sulfadiazine**
- **Triméthoprime – Sulfaméthoxazole**

# Toxoplasmosis in Transplant Recipients, Europe, 2010–2014

Florence Robert-Gangneux,[1] Valeria Meroni,[1]Damien Dupont, Françoise Botterel, José M. Aguado Garcia,[2] Marie-Pierre Brenier-Pinchart, Isabelle Accoceberry, Hamdi Akan,[2] Isabella Abbate, Katia Boggian, Fabrizio Bruschi,[2] Jordi Carratalà,[2] Miruna David,[2] Lubos Drgona,[2] Olgica Djurković-Djaković, Maria Carmen Farinas, Francesca Genco, Effrossyni Gkrania-Klotsas,[2] Andreas H. Groll,[2] Edward Guy, Cédric Hirzel, Nina Khanna, Özgür Kurt,[1] Lia Monica Junie,[1] Tiziana Lazzarotto, Oscar Len,[2] Nicolas J. Mueller, Patricia Munoz,[2] Zoi Dorothea Pana,[2] Emmanuel Roilides,[2] Tijana Stajner, Christian van Delden, Isabelle Villena,[1] Hervé Pelloux,[1] Oriol Manuel[2]

Transplantation activity is increasing, leading to a growing number of patients at risk for toxoplasmosis. We reviewed toxoplasmosis prevention practices, prevalence, and outcomes for hematopoietic stem cell transplant (HSCT) and solid organ transplant (SOT; heart, kidney, or liver) patients in Europe. We collected electronic data on the transplant population and prevention guidelines/regulations and clinical data on toxoplasmosis cases diagnosed during 2010–2014. Serologic pretransplant screening of allo-hematopoietic stem cell donors was performed in 80% of countries, screening of organ donors in 100%. SOT recipients were systematically screened in 6 countries. Targeted anti-*Toxoplasma* chemoprophylaxis was heterogeneous. A total of 87 toxoplasmosis cases were recorded (58 allo-HSCTs, 29 SOTs). The 6-month survival rate was lower among *Toxoplasma*-seropositive recipients and among allo-hematopoietic stem cell and liver recipients. Chemoprophylaxis improved outcomes for SOT recipients. Toxoplasmosis remains associated with high mortality rates among transplant recipients. Guidelines are urgently needed to standardize prophylactic regimens and optimize patient management.

EID, 2018

EXPERT REVIEW OF ANTI-INFECTIVE THERAPY
https://doi.org/10.1080/14787210.2018.1483721

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REVIEW



# Management of toxoplasmosis in transplant recipients: an update

Céline Dard[a,b], Pierre Marty[c,d], Marie-Pierre Brenier-Pinchart[a,b], Cécile Garnaud[a], Hélène Fricker-Hidalgo[a], Hervé Pelloux[a,b] and Christelle Pomares[c,d]

[a]Laboratoire de Parasitologie-Mycologie, Centre Hospitalier Universitaire Grenoble Alpes, Grenoble Cedex France; [b]Institute for Advanced Biosciences (IAB), Team Host-Pathogen Interactions and Immunity to Infection, INSERM U1209 - CNRS UMR5309, Université Grenoble Alpes, Grenoble France; [c]Faculté de Médecine, Laboratoire de Parasitologie-Mycologie, Centre Hospitalier Universitaire de Nice, 06202 Nice, France Université de la Côte d'Azur, Nice, France; [d]38043, INSERM U1065, Centre Méditerranéen de Médecine Moléculaire, C3M, Nice, France

**ABSTRACT**

**Introduction**. Toxoplasmosis is a life-threatening parasitic disease for hematopoietic stem cell transplant (HSCT) and solid organ transplant (SOT) recipients. The risk of toxoplasmosis in transplant patients mainly depends on the degree of immunosuppression, the tropism of *Toxoplasma gondii* for the grafted tissue, and the seroprevalence in the general population. Although transplant recipients with toxoplasmosis have a high mortality rate, there are neither well-defined recommendations nor a consensus for the management of this disease in these patients.

**Areas covered**. This review focuses on the management of toxoplasmosis in transplant recipients and discusses the various strategies for diagnosis, prevention, treatment, and follow-up in clinical practice. The literature search was conducted on publications in English and French using the search terms '*Toxoplasma gondii*,' 'organ transplant,' and 'transplant recipients.'

**Expert commentary**. The diagnosis of toxoplasmosis has greatly improved over the last two decades, but it is still a fatal illness. Non-specificity of the symptoms, resulting in a delay before diagnosis, and therapeutic failure are the main causes of death. The development of active treatments against cysts is one of the current challenges that will considerably improve the management of toxoplasmosis in transplant recipients by clearing chronic infection to avoid *T. gondii* reactivation.

**ARTICLE HISTORY**
Received 23 March 2018
Accepted 29 May 2018

**KEYWORDS**
*Toxoplasma gondii*; toxoplasmosis; hematopoietic stem cell transplant; solid organ transplant; preemptive treatment; prophylaxis

# Conclusion

- **Épidémiologie et diagnostic très différents selon patients SIDA/non-SIDA**

- **Nécessité de données épidémiologiques, particulièrement chez les patients non-SIDA**

# Autres protozooses d'intérêt.. (à la Prévert, hors paludisme)

Amoebose (*Entamoeba histolytica*) métronidazole, puis tiliquinol-tilbroquinol

Giardiose (*Giardia intestinalis*) métronidazole

Trichomonose (*Trichomonas vaginalis*) métronidazole

Cryptosporidiose (*Cryptosporidium hominis* ou *parvum*) nitazoxanide, rifaximine

# Autres protozooses d'intérêt.. (à la Prévert, hors paludisme)

Cystoisosporose (*Cystoisospora belli*) cotrimoxazole

Cyclosporose (*Cyclospora cayetanensis*) cotrimoxazole

Microsporidioses (fungiques ?) (*Enterocytozoon bieneusi*...) fumagilline

Leishmanioses (*Leishmania infantum*) amphotéricine B liposomale

Trypanosomoses humaines (maladie du sommeil et Chagas) pentamidine, mélarsoprol, nifurtimox