Chronic Lyme disease and associated infections: a scientific reality

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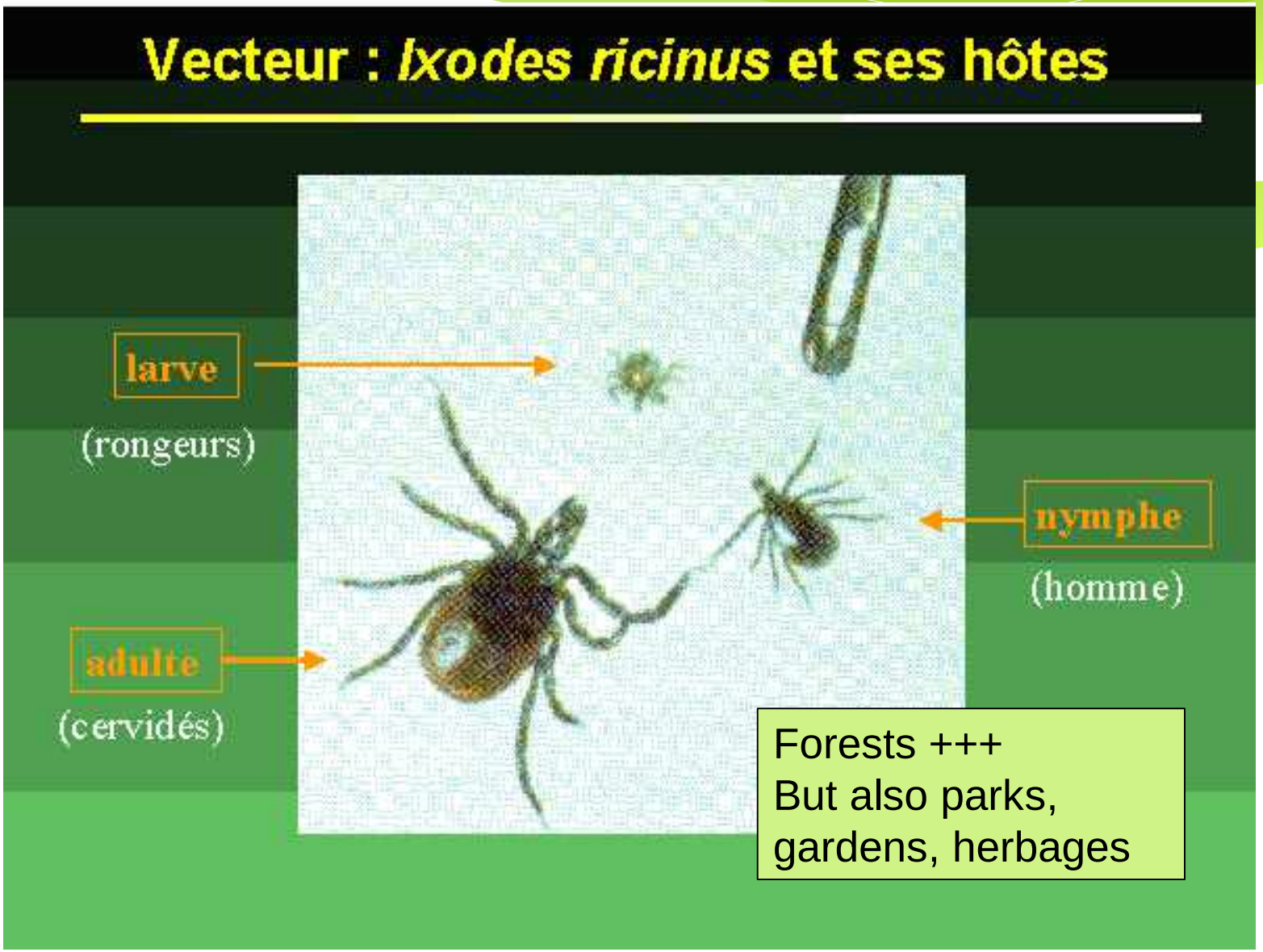
Ötzi, the Tyrol's frozen man, aged 5 300 years,
probably Corsican or Sardinian,
discovered at the border of Italy and Austria,
suffered from a borrelial disease, close to Lyme disease

Nymphs are responsible for a majority of human cases



Recall of a tick bite: in less than ¼ of cases

Erythema migrans: half of the cases
May be atypical

Recall of a tick bite before a proven Lyme disease

* Two recent studies

* **Only 16% of patients recall the bite**
  * Hatchette TF et al. *Can Commun Dis Resp*, 2014, 40, 194-208.

* **In children: 18.5% recall the bite**
  * Nogrovic LE et al. *Tick Tick Borne Dis*, 2019, 10, 694-6

Presence of erythema migrans at the early phase

* Proportion varies in the studies
* **For *Burgdorfer et al.* : Around 50%**
* Reik L Jr, Burgdorfer W, Donaldson JO. Neurologic abnormalities in Lyme disease without erythema chronicum migrans. *Am J Med*. 1986; 81: 73-8.

Erythema migrans

Erythema migrans = at least two weeks of antibiotic treatment .

Serology should not be done at that stage

Pay attention to atypical erythema migrans (EM)

* Mini-EM : size of a coin
* Oval EM
* EM without the darker outline
* Braun or purplish EM
* EM with vesicles (mimicking herpes simplex or herpes zoster)
* Painful EM (burning)
* Pruritic EM
* Hidden EM (e.g. scalp)

* **Best criterium: centrifugal evolution**

Lyme : the great imitator (la grande simulatrice)

* **Stage 2 : within days, weeks or months**
* **Stage 3 : within months to years**

  – **Disabling fatigue, migratory pains**
  subjective

  – **Chronic disorders: often objective** (not specific)
  * **Cutaneous**
  * **Neurologic, ophthalmologic**
  * **Psychiatric**
  * **Articular, muscular, osseous**
  * **Cardiac, etc...**

  – **Auto-immune syndromes**

Borrelial lymphocytoma
(ear, nipple, scrotum) : characteristic of Lyme

Acrodermatitis chronica atrophicans (ACA) = Pick – Herxheimer's Syndrome : Characteristic of Lyme

Lyme and associated crypto-infections: Very wide range of clinical conditions

* **Numerous clinical forms**

* **Large range of severity:**

  * **Benign forms**
    * Forms that cure spontaneously
      or after a short duration of antibiotic treatment
    * Asymptomatic forms (healthy carriers)

  * **Severe forms**
    * Handicap
    * Rare lethal forms
    * Suicide

Possible role of *Borreliae* and other crypto-infections in the pathogenesis of numerous chronic diseases

* Often difficult to prove, due to the lack of reliable tests
* **Chronic fatigue syndrome, fibromyalgia**
* **Auto-immune diseases**
  * Lupus
  * Multiple sclerosis
  * Rheumatoid arthritis, etc.
* **Degenerative diseases**
* **Unexplained syndromes**
  * Nevralgia, meningitis, encephalitis, paralysis, etc
  * Depression
  * Rheumatisms
  * Cutaneous, cardiac disorders …

Incidence of Lyme disease: high increase in the world

* **2007-8. Germany:** **261 cases per 100 000 inhabitants**
* **2014-16. France:**
  * **1. Alsace :** **117 cases per 100 000**
* **2016. France:**
  * 1. Limousin: **617 cases per** 100 000
  * 2. Lorraine:
  * 3. Poitou-Charentes
  * 4. Alsace : **281 cases per** 100 000
* **2016. USA, Connecticut : 1989 cases per 100 000 (=2%)**
  * Lee-Lewandrowski E et al. *Am J Clin Pathol*. 2019, 152, 6
* **South of Poland**
  * 35 fold increase in a few years

Incidence of Lyme in France: increasing

* **Increase of cases diagnosed by general practitioners**
  * **2017 : 69** cases per 100 000, around **45 000** annual cases
  * **2018 : 104** cases per 100 000, more than **67 000** annual cases
* **Results based on the current serology:** large under-estimation. Moreover, numerous *Borrelia* species and other crypto-infections not taken into account

Worrying increase of Lyme disease in the USA

← Previous Next →

United States Annual Cases of Lyme Disease for 2017 Over 400,000

Posted on November 22, 2018 by Canlyme

[CanLyme Note: The numbers reflected by the CDC in no way represent the total number of cases occurring annually in the USA. As per the CDC press release in 2013 they acknowledge that "surveillance data" only gathers about 10% of the true numbers of cases putting a more realistic total annual count for 2017 at over 400,000 cases.]

———————————————————-

In 2017, a total of 42,743 confirmed and probable cases of Lyme disease were reported to CDC, almost 9% more than in 2016. The geographic distribution of high incidence areas with Lyme disease appears to be expanding based on data reported to National Notifiable Disease Surveillance System (NNDSS). The number of counties with an incidence of ≥10 confirmed cases per 100,000 persons increased from 324 in 2008 to 454 in 2017.

Read full text ›

Posted in For Physicians, Government, International News, Lyme Controversy, Miscellaneous, News from CanLyme, Voices on Lyme and tagged annual, annually, cases of Lyme disease, Center for Disease Control, Centers for Disease Control, Lyme Disease, united states by Canlyme.

An ecologic change

In 15 years, extinction of many animals in Europe, including tick predators

Le Chasseur Français. Mai 2018

(Source : *Infos'Chasse* 67, février 2018.)

A. Durand, T. Coste, W. Schraen.

Faune sauvage

Des études dévoilent des chiffres alarmants

33 % en 15 ans

Chiffre concernant **la disparition des oiseaux** de nos campagnes, due aux pratiques agricoles, selon le CNRS et le Muséum d'histoire naturelle.

Entre 75 % et 85 %

Nombre d'insectes disparus

dans les dernières décennies, à cause, notamment, des néonicotinoïdes.

ILL. : F. DESBORDES, T. PÉTRÉFITTE (G.) A. VIAL (D.)

820 000 000 m²

C'est, selon le Syndicat des jeunes agriculteurs, **la superficie de terres agricoles** que la France perd chaque année à cause de l'artificialisation des sols.

42% des animaux terrestres, 71% des poissons et 60% des amphibiens...

... **ont disparu d'Europe** au cours de la dernière décennie.

Moins 26,8% d'alouettes...

... entre 2001 et 2017 !

B.B.

Low sensitivity of Lyme serologies : an established fact, but not recognized by many medical opinion leaders (1)

- **France: Haut Conseil de la Santé Publique 2014 :**
  - **Elisa :** 20 out of 33 tests: not reliable. **Western blot :** 4 out of 13 tests: not reliable.
  - **Recommended: Empiric antibiotic treatment for seronegative patients,** after having ruled out another diagnosis

- **Even the National Reference Centre for borrelioses in Strasbourg, 2007 recognized the existence of seronegative neuroborreliosis**
  - *Blanc, Jaulhac et coll. Neurology, 2007.*

- **Centers for Disease Control** (CDC, Atlanta)**. Change of criteria in 2011 to include « Probable cases »**

Low sensitivity of Lyme serologies : an established fact, but not recognized by many medical opinion leaders (2)

- **European CDC** (ECDC, Stockholm) . **April 2016**
  - **Warns against the « very good results » of Lyme serologies heralded** by some studies or by manufacturers
  - **Because populations are poorly defined, with many biases** (no gold standard for diagnosis)
  - **Result of serology should be confronted with clinical data**

- **Meta-analysis of the sensitivity of Lyme serologies, 2016**
  - Cook MJ, Puri BK. Imperial College, London *Int J Gen Med. 2016. 18, 9. 427-40*
  - **Mean sensitivity (all tests) : 59.5%** (30.6% à 86.2%)

Interview of Willy Burgdorfer, who discovered *Borrelia burgdorferi* (Film « Under Our Skin », 2007)

About the recommendations 2006 of IDSA (Infectious diseases society of America) **(which are obsolete):**

* It is a shameful affair
* There is a political reason
* For 30 years, money goes to those who produced always the same thing, that is nothing
* The technique of Lyme serology must be reviewed from scratch, with people who don't write their results before having done the research

Lyme serology doesn't identify other crypto-infections, some of them, well known by veterinaries

* **Dozens of other *Borrelia* species**
  * Especially *Borrelia miyamotoi*
* **Other bacteria**
  * *Bartonella*
  * *Anaplasma, Ehrlichia*
  * *Rickettsia , Coxiella burnetii*
  * *Francisella tularensis*
  * *Neoerlichia mikurensis*
* **Parasites**
  * Piroplasms : *Babesia, Theileria*

Tests for direct detection of responsible micro-organisms should be developed

* **New generations of PCR** (polymerase chain reaction)
  * Currently: lack of sensitivity

* **High throughput sequencing**

It should be allowed to evaluate in humans some diagnostic tests already used for animals in vet labs

Not reliable or not available diagnostic tests:
Many adults and children are followed by psychiatrists, because their medical condition is not understood

* **Hysteric conversion**
* **Depression**
  * infectious
  * or secondary to the rejection by physicians and relatives
* **Psychotic disorders**
* **Münchhausen ‘s syndrome**
  * Patients accused to harm themselves voluntarily
* **Münchhausen ‘s syndrome by proxy**
  * Parents accused to harm their child(ren) voluntarily

Lack of correct evaluation of anti-infective treatments:
Chronic patients are not treated

* **Several open labeled clinical studies: high efficacy of prolonged antibiotic treatment**
* **Four randomized studies (short duration) : contradictory results.** An initial exacerbation is not a failure or side-effect (Jarisch-Herxheimer reaction)
* **Not a single comparative (randomized) study of a really prolonged treatment (at least 4 month duration) of chronic Lyme disease**
* **Urgent need of funds for research**

Need for clinical research to evaluate the maintenance treatment of chronic Lyme disease

* **Published data** (in vitro studies and a few open-labeled clinical studies) **on the treatment of persistent forms of *Borrelia* :**
  * ***Antibiotics, but also:***
  * ***Anti-parasitic drugs***
  * ***Anti-fungal drugs***
  * ***Anti-leprosy drugs***
  * ***Phytotherapy***

  Metronidazole, tinidazole, hydroxychloroquine, fluconazole, clofazimine, dapsone …

  Meriläinen 2015; Sharma 2015; Feng 2014; Feng 2015a; Feng 2015b; Feng 2015c; Feng 2016; Brorson 1999; Schardt 2004; Brorson 2002; Horowitz 2016

* **Need to treat co-infections**, particularly parasitic infections (*Babesia*)

Metronidazole (Flagyl*), tinidazole (Fasigyne*)

* **Active against persistent forms of *Borrelia* plus anti-parasitic activity** (Brorson & Brorson)

* Jarisch-Herxheimer's reaction (herx) often violent
* Neurologic side-effects
* Small dosage is usually enough
  * e.g. tinidazole 500mg per day
* Short duration (in sequential treatments)
  * e.g. 8 consecutive days per month

Hydroxychloroquine (Plaquenil*)

* **Active against persistent forms of *Borrelia* plus anti-parasitic activity**
* Brorson O., Brorson S. H., *Int. Microbiol.*, 2002, 5, 25-31.
* Donta S. T., *Med. Sci. Monit.*, 2003, 9, 136-42.

* Herxes often violent
* Small dosage
  * e.g. Start with half a tablet per day (= 100 mg/d), and then one tablet 200 mg/d.
* Can be prescribed daily during several months.
* Small dose: simple ophthalmologic surveillance

Other antiparasitic drugs

* **Active against *Babesia***
  * = anti-malarial drugs
  * e.g. atovaquone-proguanil (to be ingested with meal and fat)

* **Anti-helminthic drugs**
  * Flubendazole (Fluvermal*)
  * Albendazole (Zentel*)
  * Praziquantel (Biltricide*)
  * Ivermectine (Stromectol*), (with empty stomach)

Interaction bacteria – helminths?

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Lyme Bacteria Hides Inside Parasitic Worms, Causing Chronic Brain Diseases

Recent discovery confirmed by state-of-the-art Molecular Beacon DNA probes

NEWS PROVIDED BY
Patient Centered Care Advocacy Group →
May 19, 2016, 07:00 ET

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WASHINGTON, May 19, 2016 /PRNewswire/ -- The examination of autopsied brain tissues from patients who died of serious neurological conditions has revealed that many tick-borne infections, such as Lyme disease, go undiagnosed and untreated. Board-certified pathologist, Alan B. MacDonald, MD, says his research shows "tick infections are not easily detected with routine tests, nor are they easily cured with short courses of antibiotics."

MacDonald will present his findings Thursday on Capitol Hill, in the Rayburn House Office Building, at a forum to explore the scientific, economic, and policy challenges posed by the epidemic of Lyme disease and associated tick-borne illnesses.

MacDonald found two Borrelia pathogens, including B. burgdorferi the causative agent of Lyme disease, thriving inside parasitic nematode worms, worm eggs or larvae in the brain tissue of nineteen deceased patients. These microscopic worms are endosymbionts, meaning the Borrelia bacteria dwell inside the worms. A tick bite delivers the nematode into the human body.

Treatments

* Respect the usual recommended dosages
* Avoid IV central catheters
* Biological surveillance
  * e.g. Rares cases of severe increase of transaminases at the beginning of doxycycline treatment

Anti-leprosy drugs

* **Dapsone**
* Anti-bacterial and anti-parasitic drug
* Active against persistent bacteria (leprosy, tuberculosis)
* Herxes often violent : start with 50 mg per day and then 100 mg/d
* Open labeled clinical study
  * Horowitz R., Freeman P., *J. Clin. Exp. Dermatol. Res.*, 2016, 7, doi:10.4172/2155-9554.1000345.
* Dosage of G6PD before starting treatment
* Always combine with folinic acid (25 mg/j)
* Surveillance of blood cells, especially the first days and weeks (hemolysis)
* Daily treatment during several months

Anti-fungal drugs

* **In vitro activity against persistent forms of *Borrelia***
  * Feng J et al. *Antibiotics* 2015, 4, 397-410

* **Fluconazole**

  Small open-labeled clinical study in Germany

  Schardt F. W. *Eur. J. Med. Res.* 2004; 9: 334-6.

* **Griseofulvine**
  * Old treatment for lupus
  * Surveillance of blood cells (a small dosage of 250 mg to 500 mg/d is usually enough)

Lyme and disulfiram (Antabuse*, Esperal*)

* **Anti-bacterial activity**
  * Frazier KR eta l. *J Appl Microbiol*. 2018, 126. doi.org/10.111/jam.14094

* **Report of 3 cases of severe Lyme which improved**
* 500 mg per day (smaller dosage at the beginning) Liegner KB. Antibiotics. 2019, 8, 72. doi:10.3390/antibiotics8020072

* **Many potential side-effects**
* Particularly hepatic, neurologic or visual

Phytotherapy (1)

* **Anti-infective properties**
  * Propolis
  * *Gingko biloba*

* **In vitro activity against *Borrelia***
  * Grapefruit seed extract
    * Brorson O., Brorson S. H., *Infection*, 2007, 35, 206-8.

Phytotherapy(2)

Feng J, Zhang Y. et al.

Front Med 2017, 4, 169. Antibiotics 2018, 7, 89

- **Active in vitro against persistent forms of *Borrelia***
  - Lemon grass
  - Wintergreen
  - *Artemisia*
  - Cat's claw
  - Chili pepper
  - Thyme
  - Eucalyptus

- **Sterilize cultures of *Borrelia***
  - Oregano (carvacrol)
  - Cinnamon bark
  - Clove
  - Garlic
  - *Cryptolepis sanguinolenta*

Chronic Lyme disease is proven, however denied by opinion leaders in the USA and Europe

* **Signs and symptoms often persist after three week antibiotic treatment**
  * **Persistence in 16 to 62% of cases**
  * ***6 scientific references***
* **Persistence of *Borrelia* in animals**
  * **Even after several months of antibiotic treatments**
  * ***7 scientific references***
* **Persistence of *Borrelia* in culture or PCR in humans**
  * **Even after after antibiotic treatments of late stages of Lyme disease**
  * ***14 scientific references***

France, September 2016: a National plan is launched by the Minister of Health

* Strategic axis 1
  * **Improve the surveillance of vectors and the measures against ticks in a « WHO one health » approach** (humans/animals)
* Strategic axis 2
  * **Enhance surveillance and prevention of tick-borne diseases**
* Strategic axis 3
  * **Improve and homogenize the management of patients**
* Strategic axis 4
  * **Improve diagnostic tests**
* Strategic axis 5
  * **Develop research on tick-borne diseases**

Strategic axis 3
Improve and homogenize the management of patients

- **Multi-disciplinary group of experts**
- Under the auspices of the Haute Autorité de santé, HAS **(High Authority for Health)**

- **Including representatives of:**

  - **Medical societies** (physicians from several specialties, microbiologists, general practitioners)
  - **National reference centre** for borreliosis
  - **Patients**
  - **Lyme doctors** from the Federation FFMVT

2015: French Federation against Tick-borne Diseases (FFMVT)

- **Associations** (patients and supporters) **+ College of physicians and researchers + Scientific council**

- **Advocacy based on scientific arguments and medical literature**
  The evidence is on our side

- **Increased a lot consideration** by
  - media
  - politicians

- With a **positive image**

Principal progresses of the French recommendations of the High Authority for Health (HAS)

* **The low quality of serologic tests is recognized**

* **A syndrome is defined: SPPT (Syndrome persistant polymorphe après une possible piqûre de tique, Persistent polymorphic syndrome after possible tick-bite),** including other crypto-infections.
* Close to the American PTLDS (post-treatment Lyme disease syndrome)
* This SPPT is diagnosed clinically

* **Response to an antibiotic empiric treatment is a diagnostic tool**

* **Possibility to treat for longer durations,** under the surveillance of authorities, by registering data for research

Reference centres on tick-borne diseases: **the hope**

* **Recommendation of good practice of the High Authority for Health (HAS) 2018.**

* After the one month empiric antibiotic treatment, in case of persistence of signs and symptoms, **possibility to treat for longer durations with other drugs**

* Any general practitioner should define the best management with a Clinical reference centre

* *« These Centres **must** include representatives of Lyme patients in their steering committee »*

Reference centres on tick-borne diseases: **the anger**

* **Decision of the ministry of Health: DGS / DGOS 2019**

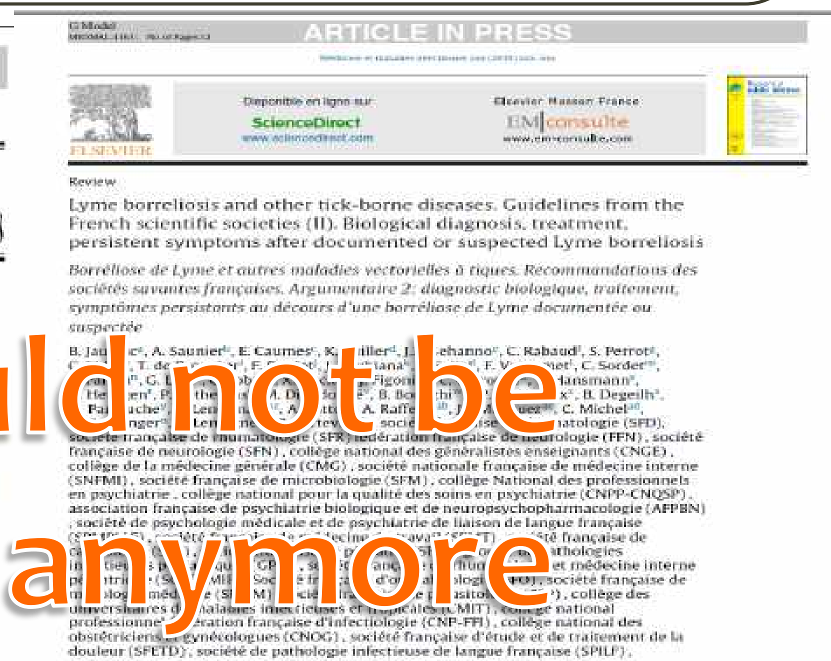
* Five Clinical reference centres are accredited, plus Competence centres

* These five centres publicy reject the official Recommendation of the High Authority for Health (HAS) 2018 and publish new « Advices » with the French infectious disease society (SPILF) 2019 (identical to those of 2006)

* No representatives of Lyme patients in their steering committees = patients feel betrayed. Violation of health democracy

Misinformation by the National reference centre for borreliosis in Strasbourg and by the French infectious diseases society (SPILF). May-June 2019

Numerous scientific references are not taken into account
Exclusion of the French Society of Immunology (SFI)
Exclusion of patients' advice. Poor copy of the obsolete « Consensus » of 2006
~~Guidelines~~: « Expert advices »
Not officially recognized



Denial should not be authorized anymore

Offical European statements on Lyme borreliosis

* **European parliament and Council of Europe. Decision 1082/2013**

  Lyme borreliosis deemed as

  « Serious cross-border threat to life »

  « Life-threatening or otherwise serious hazard to health … »

  May necessitate coordination at Union level

* **ECDC** (Stockholm), August **2017**

  Lyme: among the 30 most threatening diseases of public health importance (Annex 1, step 2). Not ranked (randomized order)

* **European Parliament, 15 November 2018**

  Unanimous vote of a Resolution asking UE to take political decisions

US federal report on Lyme disease and co-infections

- **US Department of Health and Human Services (HHS):**
- Tick-borne disease working group
- Online since **9 May 2018**

- **Official recognition of:**
  - the lack of good diagnostic tests
  - the insufficient recognition of co-infections
  - the absence of good clinical trials to evaluate treatments
  - the persistence of signs and symptoms and of bacteria

- **Need to fund research**

- https://www.hhs.gov/sites/default/files/tbdwg-report-to-congress-2018.pdf?fbclid=IwAR1u5BTMGMUMCIdMOfudGAqChW1psJL421l76FXWWn4u-YYh2edmRR0LHyw

« ~~Guidelines~~ » Advice IDSA 2019

* Infectious diseases society of America
* Regression compared to the obsolete 2006 guidelines
* Not evidence based
* Denial should not be authorized anymore

Prevention of tick bites

Europe on the move

* **First European Crypto-infections Conference**
* Dublin, Ireland. 31 May-1 June 2019

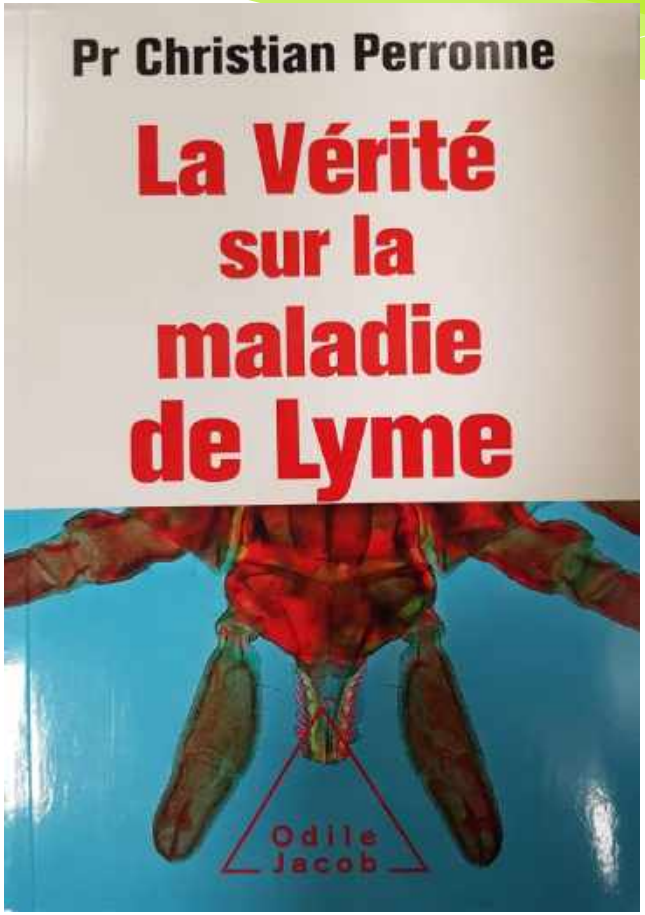
* Second conference planned in March 2020
* Need for a European medical society

Odile Jacob publisher, Paris, January 2017

« *The Truth about Lyme Disease* » (in French)

New updated edition : October 2019

English version: May 2020



Grazie

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Lyme : signs and symptoms often persist after three weeks of antibiotic treatment

* **Persistence of signs and symptoms : 16 à 62%**

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* **Cairns & Godwin.** Post-Lyme borreliosis syndrome: a meta-analysis of reported symptoms. **Int J Epidemiol. 2005; 34: 1340-5.**

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Persistence of *Borrelia* in animals

Even after several months of antibiotics

- **Straubinger et al.** Persistence of *Borrelia burgdorferi* in experimentally infected dogs after antibiotic treatment**. J Clin Microbiol. 1997; 35: 111-6**
- **Straubinger.** PCR-based quantification of *Borrelia burgdorferi* organisms in canine tissues over a 500-day postinfection period**. J Clin Microbiol. 2000; 38: 2191-9**
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- **Hodzic et al,** Persistence of *Borrelia burgdorferi* following antibiotic treatment in mice**. Antimicrob Agents Chemother. 2008; 52: 1728-36**
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Persistence of *Borrelia* in culture or by PCR in humans after antibiotic treatment of late stages of Lyme disease (1)

* **Haupl et al.** Persistence of *Borrelia burgdorferi* in ligamentous tissue from a patient with chronic Lyme borreliosis. **Arthritis Rheum. 1993; 36: 1621-6.**
* **Lawrence et al..** Seronegative chronic relapsing neuroborreliosis. **Eur Neurol. 1995; 35: 113-7.**
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Culture ou PCR *Borrelia* positive chez 40% des malades en rechute

Persistence of *Borrelia* in culture or by PCR in humans after antibiotic treatment of late stages of Lyme disease (2)

* **Pfister et al.** Randomized comparison of ceftriaxone and cefotaxime in Lyme neuroborreliosis. **J Infect Dis. 1991; 163: 311-8.**
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* **Clinical and microbiological persistence is demonstrated**