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Post-bacterial infection chronic fatigue syndrome is not a latent infection

Le syndrome de fatigue chronique post infection bactérienne n'est pas une infection latente

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ABSTRACT

Post-infectious chronic fatigue syndrome is a public health problem. Etiologies and physiopathological mechanisms are unknown. Some viruses are known to be involved in post-infectious chronic fatigue syndrome, but the role of bacterial infection is still questionned, especially in cases of post-treatment Lyme disease syndrome where subjective symptoms are regularly attributed to the presence of the dormant bacterium without scientific evidence.

However, the medical experience of recalcitrant infections, relapses, and reactivations questions the role of “dormant bacteria” in asymptomatic latent infections as well as in subjective symptoms. We summarized scientific literature data on post-bacterial infection chronic fatigue syndrome, the role of dormant bacteria in latent infections, and bacterial asymptomatic carriage. Subjective symptoms described in post-infectious chronic fatigue syndromes are still misunderstood and there is no evidence suggesting that such symptoms could be related to dormant bacterial infection or carriage of viable bacteria. Psychological trauma may be part of these subjective symptoms. Post-infectious chronic fatigue syndrome could nonetheless be due to unknown microorganisms. Antibiotic treatment is not required for latent infections, except for latent syphilis and latent tuberculosis infections to prevent, after the primary infection, progression to the secondary or tertiary stage of the disease.

Résumé

Le syndrome de fatigue chronique post-infectieux représente un enjeu de santé publique. Ses étiologies et mécanismes pathophysiologiques restent inconnus. Certains virus sont impliqués dans le syndrome de fatigue chronique post-infectieux, mais le rôle de l'infection bactérienne est encore remis en question notamment dans le cadre du « Lyme tardif post-thérapeutique » lors duquel les symptômes subjectifs sont régulièrement attribués à la présence de la bactérie dormante, sans preuve scientifique.

Toutefois, l'expérience médicale des infections réfractaires au traitement, des rechutes et des réactivations met en doute le rôle de la « bactérie dormante » dans les infections latentes asymptomatiques ainsi qu'en cas de symptômes subjectifs. Nous résumons les données scientifiques issues de la littérature sur le syndrome de fatigue chronique post infection bactérienne, le rôle des bactéries dormantes dans les infections latentes et le portage bactérien asymptomatique. Les symptômes subjectifs décrits en cas de syndromes de fatigue chronique post-infectieux restent peu compris et aucune donnée ne suggère que ces symptômes peuvent être liés à une infection bactérienne dormante ou au portage de bactéries viables. Un traumatisme psychologique pourrait en partie expliquer ces symptômes subjectifs. Le syndrome de fatigue chronique post-infectieux pourrait néanmoins être dû à des micro-organismes inconnus. Aucun traitement antibiotique n'est requis en cas d'infections latentes, à l'exception d'une syphylis latente ou d'une infection tuberculeuse latente afin de prévenir la progression vers les stades secondaires et tertiaires de la maladie, après l'infection primaire.

I. Introduction

Chronic fatigue syndrome is defined by unexplained disability syndrome and a combinaison of non-specific subjective symptoms including fatigue, headache, musculoskeletal pain, neurocognitive disorders, sleeping disorders, mood disorders, and even respiratory tract disorders. Chronic fatigue syndrome represents a major public health problem, but its etiologies remain poorly understood. Post-infectious chronic fatigue syndrome has been reported after viral infections such as Epstein-Barr virus infection, Chikungunya virus infection, and hepatitis A and B infections [1, 2, 3]. Regarding bacterial infections, post-infectious chronic fatigue syndrome may be suspected after brucellosis, Q fever caused by *Coxiella burnetii*, and Lyme disease caused by *Borrelia burgdorferi* group (*Borreliae).* However, no evidence of a progressive infection can explain chronic fatigue syndrome (no clinical or biological inflammatory syndrome, no evidence of bacterial multiplication, and no evidence of antibiotic effectiveness). Post-infectious chronic fatigue syndrome therefore remains a crucial and unsolved issue. The question currently raised is whether latent infection could be responsible for subjective syndrome, as told in the post-treatment Lyme disease syndrome.

However, the medical experience of recalcitrant infections, relapses, and reactivations observed in cases of bone and joint infections even decades after the primary infection, underlines that some bacteria could persist in a dormant stage. These dormant bacteria remain quiescent and viable, without any clinical manifestation. Several factors can promote reactivation such as immunosuppression and pregnancy, but no reactivation factors can sometimes be identified. Some bacterial infections occur in several stages, with latency periods in-between some stages. This is the case for Lyme disease, tuberculosis, and syphilis. The primary infection is self-limiting, but if left untreated the disease can

quiescently progress to secondary or tertiary manifestations. Finally, the identification of pathogenic bacteria in asymptomatic and healthy individuals, as asymptomatic carriage, led us to re-interrogate Koch's postulates.

To find out whether these latent infections, dormant bacteria, or asymptomatic carriages may have a role in post-infectious chronic fatigue syndrome, we performed a literature review. We searched Medline and Googlescholar databases for references with no language restriction and no restriction of publication time nor status, with the following keywords: dormant bacteria, latent infection, post-infectious chronic fatigue syndrome, chronic fatigue syndrome, asymptomatic carriage, post-treatment lyme disease syndrome, post-Q fever fatigue syndrome, latent tuberculosis, *Mycobacterium tuberculosis*, *Brucella* spp., *Tropheryma whipplei*, *Bartonella* spp., *Staphylococcus aureus.* A total of 119 references were included in the final qualitative synthesis.

II. Post-bacterial infection chronic fatigue syndrome

1. Coxiella burnetii: the Q fever fatigue syndrome

First described in 1992, the Q fever fatigue syndrome (QFS) is a health challenge as it is responsible for impaired quality of life and absenteeism [4, 5]. QFS is characterized by subjective symptoms for at least six months after acute Q fever. It is responsible for significant disability in daily living and it is not associated with objective symptoms nor organic lesions [6, 7, 8]. The diagnosis should rule out other somatic and psychiatric etiologies of chronic fatigue syndrome. QFS also does not correlate with the anti-*C. burnetii* phase I IgG levels, which are insufficient and erroneous to conclude to the persistence or lack of persistence of the infection.

In the Netherlands, after the 2007-2011 epidemiological outbreaks, QFS developped in 20% of patients who had been diagnosed with acute Q fever as compared with 4% of healthy controls [5]. In Australia, QFS developped in 28% of patients who had been diagnosed with acute Q fever versus 0% of controls [9]. Pentillas *et al.* provided the first broad description of QFS in Australia, but their report can be questioned as they included patients presenting with objective symptoms (diarrhea, swollen superficial lymph node) [10]. Just like post-treatment Lyme disease syndrome (PTLDS), the persistence of living microbes has been suggested to be involved in QFS, but never confirmed [10]. A fundamental and dangerous confusion may thus be observed between latent infections and QFS. This confusion leads to misdiagnosing *C. burnetii* persistent latent infection as illustrated by the fatal case recently reported by Sudocheva *et al*.: a 19-year-old man was diagnosed with post-Q fever fatigue syndrome and died from disseminated *C. burnetii* infection 10 years after acute Q fever infection [11, 12]. *C. burnetii* was identified by immunohistochemistry (IHC) and polymerase chain reaction (PCR) targeting the COM1 and IS*1111* sequences in all post-mortem investigated organs [11]. Marmion *et al.* also reported two cases of patients misdiagnosed with chronic fatigue syndrome instead of persistent *C. burnetii* endocarditis (one fatal case) [9, 13]. These three cases argue in favor of long-term latent and asymptomatic *C. burnetii* infection. This infection is different from QFS as it only affects patients presenting with subjective signs and symptoms, with no detected living bacteria. Experimental studies on tissues distinguished living bacteria from dead bacteria using fluorescence *in situ* hybridization targeting the bacterial ribonucleic acid [14]. As *C. burnetii* was not isolated from these blood samples in case of QFS, persistent *C. burnetii* cell components are probably residues of the original heavy seeding during bacteremia rather than a renewed production of viable bacteria [8]. The long-term persistence of non-viable *in situ* or circulating *C. burnetii* cell components including antigens or DNA is the sole biological finding currently correlating with these subjective

symptoms. The circulation of these bacterial cell components could result in an altered cell immunity and in an altered cytokine production [13, 15, 16, 17]. The subsequent ongoing production of pro-inflammatory cytokines could then be responsible for fatigue. Patients presenting with QFS were described as differing in the frequency of HLA-DRB1*11 carriage and the 2/2 genotype of the IFNγ intron 1 microsatellite when compared with controls [18]. In addition, cytokine release pattern of peripheral blood monocyte cells of QFS patients was reported as aberrant with an increased IL-6 release, a decreased level of IL2 release, and an increased INFγ and CXCL10 production [19].

Just like PTLDS, it is unknown whether QFS is a direct consequence of the non-viable or viable bacteria or if its origin is psychological. Predictors of QFS are contradictory, and factors such as female sex and young adult have been associated with QFS [8]. The severity of the acute illness as well as preexisting health problems and hospitalization have been reported as QFS predictors [20, 21].

2. Borrelia burgdorferi and post-treatment Lyme disease syndrome

Post-treatment Lyme disease syndrome (PTLDS) is characterized by the late onset of musculoskeletal symptoms and antibiotic treatment failures. PTLDS is estimated to affect 10% to 20% of patients treated with antibiotics effective against Lyme disease [22, 23]. PTLDS is a public and political challenge as compared with *C. burnetii* infection, but few studies have been conducted to identify *B. burgdorferi* cell components or to understand the physiological and immune mechanisms involved in PTLDS [24]. Picha *et al*. performed a study with *B. burgdorferi*-infected patients, and identified *B. burgdorferi* DNA up to six months after the administration of an effective antimicrobial treatment. However, this result does not indicate the presence of living bacteria, and all patients with a positive *B. burgdorferi* PCR did not present with subjective symptoms

[25, 26]. Autoimmune diseases are believed to be involved in patients diagnosed with PTLDS. Maccallini *et al.* hypothetized that such patients exhibited auto-immunity against γ-enolase, the neuron-specific isoenzyme of the glycolytic enzyme enolase [27].

Cabello *et al.* explained that in the absence of sterilizing immunity a strong antibody response was observed. They suggested that *B. burgdorferi* is located in a niche where it could be protected from the adaptive immune response [28]. The extracellular matrix, rich in collagen such as tendon and ligaments, was suspected to be the niche of *B. burgdorferi* in mice [28]. Crossland *et al.* recently identified persistent non-viable *Borrelia* in the central nervous system, joint-associated tissues, and urinary bladder of rhesus macaques following doxycycline therapy [29]. Hodzic *et al.* demonstrated that after ceftriaxone therapy in a mouse model, *B. burgdorferi* could not be cultured from tissues while low copy number of specific DNA sequences could be detected two, four, and eight months after treatment completion [30].

Interestingly, Iyer *et al.* demonstrated *in vitro* that *B. burgdorferi* could not be cultured three days after ceftriaxone antibiotic treatment, but positive *B. burgdorferi* DNA was detected up to 56 days after antibiotic treament [26]. These results are at odds with experimental data reported by Caskey *et al.* showing the doxycycline inability to kill quiescent *B. burdgorferi*, which newly developed after antimicrobial therapy [31]. The lack of studies in humans does not allow scientific support for the responsibility of quiescent *B. burgdorferi* or dormant bacteria in PTLDS.

3. Brucella spp. and post-infectious fatigue syndrome

Chronic fatigue syndrome after *Brucella* infection has been reported in patients with poor health, musculoskeletal pain, depression, or anxiety without any infectious focus of the disease [32]. However, the definition and description of persistent subjective symptoms after brucellosis is

often mistaken with chronic brucellosis. Historically, antigen therapy was suggested to patients presenting with chronic brucellosis following antibiotic therapy [33, 34, 35]. The term “post-brucellosis fatigue syndrome” could be more appropriate to differentiate subjective symptoms without detectable organic lesions following infection from chronic persistent *Brucella* infection.

Some studies focused on post-brucellosis disease. The persistent detection of *Brucella* spp. DNA after an effective antibiotic therapy was initially related to relapses. Castano *et al.* recently identified the presence of *Brucella* spp. DNA in the blood and serum of patients presenting with persistent focalized infection, with non-focal disease and with subjective symptoms. This finding was even observed in the group of asymptomatic subjects with a history of brucellosis, but not in the control group [32]. The authors reported that the proportion of individuals with *Brucella melitensis* DNA was significantly higher in symptomatic non-focal disease patients (patients with subjective symptoms and without identified focus) than in asymptomatic subjects [32]. *Brucella abortus* has been widely used to study chronic fatigue syndrome in animal models. An impaired mouse running activity has been described when animals were inoculated with *B. abortus* antigens [36]. Potential oxidative stress and immunological activation as assessed by an increase in tumor necrosis factor alpha are involved in chronic fatigue syndrome induced by *B. abortus* [37].

Whether for *Brucella* spp., *C. burnetii*, or *B. burgdorferi*, the persistence of bacterial DNA copies in blood samples remains poorly understood. We do not know if these DNA sequences are associated with subjective symptoms and the expression of viable dormant bateria.

III. Dormant bacteria and latent infection: a reversible aliveness

In 1944 Joseph Bigger led the founding stone of the concept of "dormant bacteria", with a microbiological definition. He observed that penicillin lysed a growing population of *Staphyloccocus* spp. but only a small proportion, although not resistant to antibiotics and not in a fission stage, survived [38]. This data suggested that penicillin was only effective in dividing bacteria. "Dormant bacteria" are characterized by a non-growing and non-replicating stage, by viability (but unable to grow on usual culture media), and by tolerability to stress including stress-induced antibiotics [39, 40]. Consequently, they could be responsible for antibiotic treatment failure to eradicate the infection. At the "dormant" stage, bacteria are also non-virulent and bypass the innate immune system response. These bacteria could return to growth and normal activity when original conditions are restored [39].

1. *Staphylococcus aureus* bone and joint infection

Since the description of *Staphylococcus aureus* as a "dormant" bacterium, mechanisms used to achieve its intracellular persistence have been partially identified. *S. aureus* small colony variant (SCV) is a quiescent metabolic state related to persistence, recurrence, and antibiotic resistance [40–42]. Small colonies are also distinguished from usual *S. aureus* colonies on agar plates by their decreased pigmentation and reduced hemolysis [40–42]. *S. aureus* SCVs are then characterized by a low metabolic activity. Proctor *et al.* showed that *S. aureus* SCVs settled in an intracellular niche and that 25% of the initial inoculum switched to SCVs [43, 44].

In humans, *S. aureus* SCVs were recovered from abscess, bone and joint, blood, catheters, heart, and respiratory tract. All presented auxotrophic defects accounting for their low metabolic activities [45]. Non-professional phagocytic cells such as endothelial cells, epithelial cells, fibrobasts, osteoblasts, and keratinocytes were identified as host cells for intracellular persistence of *S. aureus* SCVs [42]. *In vitro*, keratinocytes and

endothelial cells infected with *S. aureus* SCVs did not present any sign of damaged cells unlike cells infected with the usual *S. aureus* which underwent cell apoptosis or necrosis [42]. This data supports the role of these cells as latent niches for *S. aureus* infection.

2. Latent bacterial infection
    a. Syphilis

Treponema pallidum is responsible for syphilis and is characterized by its ability to invade the human body and escape the immune system. It is also characterized by a latent stage following the secondary stage and preceding the tertiary stage of the infection [46]. Early latent syphilis is defined by a positive serology without clinical symptoms. Late latency may start one or two years after exposure and may last up to several decades. It is estimated that 15-40% of untreated individuals develop tertiary syphilis characterized by cardiac, neurological, skin, and bone involvement with destructive syphilitic gumma, hemiparesis, aphasia, aortitis, aortic aneurysm, and congestive heart failure or coronary disease [46]. As a global worldwide re-emerging disease, latent *T. pallidum* infection is still challenging physicians because of two critical complications. In immunocompromised hosts, malignant syphilis has been described as a severe cutaneous complication of syphilis in AIDS patients, and we recently observed neurological syphilis involvement in HIV-infected patients with low CD4 level (<350/mm^3). These reports demonstrated that immunosuppression is a factor promoting awakening of the latent form [47, 48]. Pregnant women presenting with latent syphilis can transmit the infection *in utero* leading to recent dramatic outbreaks of congenital syphilis in Australia and the United States [49–51, 52].

The detection of *T. pallidum* DNA in patients with latent stage of the disease was only observed in blood and ear scraping [53]. Only former animal studies aimed to understand *T. pallidum* quiescent surviving. One century ago, Pearce and Brown described the rabbit's large and

indurated lymph nodes (inguinal, popliteal, submental, auricular, axillary, and large flanck) as the latent niches of the bacterium [54]. Inoculation of the emulsion of resected asymptomatic lymph nodes induced the development of syphilis in previously uninfected animals [54]. In another experimental work, Collart *et al.* showed that corticosteroids reactivated latent syphilis in two of 12 rabbits [55]. During this latent stage, the authors pointed out the morphological transformation of *Treponema* [55]. *T. pallidum* is supposed to survive extracellulary, in areas rich in connective tissues and relatively inaccessible to circulating immune cells (tunica albuginea, tunica media of the aorta, testes) [55]. Cerebrospinal fluid and lymphoid sites act as reservoirs for spirochetes, and maintain the disease in a quiescent state. The latent stage is characterized by the absence of symptoms and the reactivation may be promoted by immunosuppression or other hitherto unknown factors.

b. Lyme disease

Borrelia burgdorferi infection is characterized by symptom-free stages and several years may go by between the early localized and late disseminated stages [56]. There is no documented case of bacterial presence at the latent stage. Reports rather focus on descriptions of the secondary or tertiary stage of the infection [57, 58]. Several animal models tried to identify the persistent niche of *B. burgdorferi* but most of these models focused on explaining PTLDS in mice, dogs, and macaques, and provided evidence of persistent bacteria by immunofluorescence and PCR after antibiotic therapy [29]. As previously discussed, the presence of *B. burgdorferi* DNA does not indicate bacterial viability.

As *B. burgdorferi* is probably present at a latent stage before the tertiary stage of the infection, its niche has not been identified. Although speculative works using mathematical models studied dormant properties of *B. burgdorferi in vitro* and *in vivo,* only migratory birds have been reported as able to carry *B. burgdorferi* at a latent stage for several months [59, 31]. Moreover, immunosuppression has not been described as

favoring the reactivation of *B. burgdorferi*, nor has it been described as influencing the acute phase of the infection [60]. This was anecdotically described for *B. miyamotoi* reactivation in a patient presenting with follicular lymphoma treated with chemotherapy [61]. Finally, evidence for latent Lyme disease reactivation in immunocompromised patients is scarce.

c. Tuberculosis

Mycobacterium tuberculosis is a global health challenge, with 10.4 milion new cases diagnosed in 2016 and 1.3 million deaths [62]. It has been estimated that one third of the global population carries latent *M. tuberculosis* infection – representing an enormous reservoir of potential tuberculosis cases – after initial infection usually occurring during childhood [63]. The infection is almost kept under control by the immune system and leads to disease in only 10% of cases [63]. Hundreds of million of tuberculosis reactivation cases are expected in future decades, representing a public health challenge [62]. The term "latent tuberculosis" was coined by Clemens von Pirquet (the inventor of the tuberculin skin test [TST]) in 1907. He described children with a positive TST presenting without any clinical symptoms [64]. The current definition of latent tuberculosis combines a positive TST or positive interferon gamma release assay without clinical nor active radiological signs of the disease. Patients presenting with latent tuberculosis cannot transmit the disease but are subject to reactivation, with an estimated 2% to 23% of lifetime risk in developped countries [65].

Reactivation of *M. tuberculosis* is triggered when the host's immune response is weakened or suppressed. Patients with high risk of reactivation have HIV co-infection, lymphoma, leukemia, neck cancer, or underwent transplantation or chemotherapy, or received TNF-alpha inhibitor

treatment [66, 67, 68, 69]. Patients with a moderate risk of reactivation are patients with diabetes mellitus and patients treated with systemic glucocorticoids [70, 71]. The success of *M. tuberculosis* is first based on its capacity to avoid the microbicidal activity of macrophages [72, 73]. The reduction of MHC II expression by macrophages prevents the recognition of infected macrophages by CD4+ T lymphocytes and the activation of the adaptive immune response especially. In addition, *M. tuberculosis* inhibits the phagolysosome fusion avoiding the vacuole acidification and clearance of the ingested microorganism. It has been demonstrated that *M. tuberculosis* further prevents host cell apoptosis by enhancing the release of the membrane-bound TNFR2 receptors and by upregulating the expression of Mcl-1 (Bcl2 family protein) [74]. In response to environmental stress, *M. tuberculosis* mycobacteria shut down and close tight causing thickening and decreased permeability of the cell wall [74]. *M. tuberculosis* turns down its own central metabolism and survives for a long time in a dormant non-replicating stage. Interestingly, the toxin-antitoxin system is involved in the persistence of *Mycobacterium* sp. in a dormant non-replicating stage [74]. At a physiological stage, the long-lived "toxin" protein is neutralized by the short-lived "antitoxin" protein. However, at the dormant stage *M. tuberculosis* represses the expression of the antitoxin protein, which results in the accumulation of the "toxin" protein [74]. The toxin protein, as a ribonuclease, cleaves free and ribosomal-bound single-stranded mRNA, inhibiting protein synthesis and bacterial growth [74]. A group of proteins called the resuscitation promoting factors (encoded by *rpf* genes) also induce *M. tuberculosis* out of the dormant stage [75]. When the stress agent is removed, *rpf* genes are activated, proteins are produced, and the bacterium is able to re-enter a replicative phase [75]. The well-organized granuloma confers a confined environment for the survival of the bacterium and *Mycobacterium* can be released as a serpentine cord in the granuloma, a morphological presentation which is not recognized and not phagocyted by macrophages [75].

The cellular niches of *M. tuberculosis* have been revisited at the beginning of this century by Hernandez-Pando *et al.*. They identified *M. tuberculosis* DNA in macrophages and in non-professional phagocytic type II pneumocytes, endothelial cells, and fibroblasts [63]. Neyrolles *et al.* observed non-replicating *M. tuberculosis* mycobacteria within adipocytes where they exhibited increased resistance to isoniazid and a diminished resistance to pyrazinamide. This result is consistent with the hydrophilic property of isoniazid [76]. Furthermore, Ayyappan *et al.* showed that in experimentally infected rabbits, *M. tuberculosis* modulated differently the adipocyte signalling according to the latent or active infections [77].

Nonetheless, animal models tried to reproduce latent *M. tuberculosis* infection, but none was truly contributory and representative as "latency" was drug-induced [78, 79].

d. Rickettsiosis, the Brill-Zinsser disease

Rickettsia prowazekii is responsible for epidemic typhus and is transmitted by body lice. It has deeply marked the history of medicine, war, famine, and migration [80]. In addition to its typical presentation including abrupt fever, rashes, and headaches, recurrent presentations of epidemic typhus have been reported such as Brill-Zinsser disease [80]. First described in 1934, Brill-Zinsser disease is unrelated to louse infestation but also presents as fever, headache, and cutaneous rash [81]. The reactivation of *R. prowazekii* can occur even 40 years after the acute infection. Bacteremia can be detected and IgG antibodies serum reactivation assessed, with no detectable IgM antibodies, demonstrating the reactivation of the infection [82]. It has been hypothetized that after the initial contamination, the bacterium spreads via the lymphatic route and blood towards endothelial cells [80]. Some authors showed that *Rickettsia* spp. could be found in lymph nodes years after the acute infection,

suggesting this lymphoid organ as a niche for bacterial survival and dormancy [83]. In mice, adipocytes were demonstrated to be the specific cell type for *R. prowazekii* dormancy [84]. Latent typhus infection was identified in two animal models: mice and cotton rats. *R. prowazekii* was reactivated using dexamethasone, which induced an anti-inflammatory effect on the host's innate immune response [82, 83]. However, the mechanism of *R. prowazekii* dormancy and reactivation in humans has not been established.

e. *Brucella* spp.

Brucella spp. are able to induce latent infections [86, 87]. *Brucella* spp. reactivation as a gall bladder infection has been reported 28 years after primary infection in a non-endemic region [86, 87]. Immunossupression such as chemotherapy (cyclophosphamide, vincristine, methotrexate, 5-fluorouracil, etoposide, doxorubicin, and cisplatin and dexamethasone), transplantation, and anecdotically during pregnancy, has been reported [88–90]. Although the latency niche has not been well-established in humans, in animals bacteria were isolated from vaginal secretion and milk of asymptomatic sheep up to three years after the infection of the flock [91]. Rats born from *Brucella abortus*-infected mothers have been reported as latent carriers of *Brucella*. Cervical lymph nodes are described as an initial efficient trap for *Brucella*, and were also identified as a potential reservoir niche for chronic pathogen persistence [92]. *Brucella* can survive for a while in the host cell macrophages and dendritic plasmacytoid cells. It highlights their ability to induce chronic and life-long infections. Just like *C. burnetii* and *M. tuberculosis*, *Brucella* spp. can prevent apoptosis of the macrophage, through Bcl2A1 upregulation [93]. *Brucella* thus persists in tissues and induces granulomatous inflammation. The latter inflammation restricts bacterial replication but is insufficient to kill the bacterium [94]. In addition to macrophages, dendritic cells and microglia, non-phagocytic cells such as fibroblasts, epithelial cells, osteoblastic cell lines, trophoblasts, and astrocytes have

been suggested as niches [94]. Jacob *et al.* have shown that *Brucella* spontaneous smooth small colony variants were characterized by a less effective clearance from spleen and liver in experimentally infected mice [95].

f. Coxiella burnetii

The latent *C. burnetii* infection stage has been suspected after relapses were observed in patients presenting with an apparent Q fever recovery [96–98]. The placenta was described as a latent niche for *C. burnetii*, insofar as the bacterium was isolated from the placenta of women with a history of Q fever, but without clinical manifestations of the disease [99–101]. The latent presentation could be reactivated by immunosuppression or pregnancy and could infect placenta, heart valve, vascular, bones, or liver.

In the 1940s, it was demonstrated that *C. burnetii* persisted in animals after an initial clinical or subclinical infection. Its persistence was first explored in guinea pigs where the rickettsial agent of American and Australian Q fever was present in various organs up to 110 days after the primary infection and after defervescence [102]. The experimental works of Sidwell described the latent infection as an unapparent infection in which host equilibrium is established. *C. burnetii* reactivation was described with deep infectious focus after whole body irradiation, or after repeated injections of corticosteroids in guinea pigs and, to a lesser extent, in mice three months after the primary *C. burnetii* infection [96, 103]. In a study inoculating *C. burnetii* in pregnant sheep (early stage of pregnancy), the bacterium was detected up to 13 weeks in the bone marrow, spleen, liver, kidney, and in placenta just before parturition and at 20 weeks post delivery [17, 104]. This data argues in favor of the reactivation of a cryptic infection and of the existence of latent niches for *C. burnetii*.

The biological form of the persistent organism is unknown. It was hypothesized that *C. burnetii* survives in macrophages as resistant small-cell variants. In a mouse model, Bechah *et al.* demonstrated the persistence of *C. burnetii* in abdominal inguinal and dorsal adipose tissues and in macrophages up to four months after the primary infection [105]. *C. burnetii* inhibits the fusion with lysosome in the late phagosome of cultured adipocytes, and inhibits apoptosis [105]. Further clinical investigations are required to identify the organ of latent *C. burnetii* infection and the biological form of the persistent organism.

All infectious agents mentioned in the present article are able to induce primary infection and persistent focalized infection. The primary infection could be separated from the persistent focalized infection by a free phase, during which no clinical symptoms are observed. This phase could be called the latency phase. Table 1 summarizes the site of latency and the evidence for bacterial survival without clinical symptoms in humans.

IV. Bacterial carriage without symptoms

1. *Bartonella* species

Unlike bacterial DNA detection in asymptomatic patients with a history of infectious diseases, *Bartonella* spp. were isolated from the blood of asymptomatic donors. Bacteria were identified by culture and real-time PCR from the blood of 3.2% of asymptomatic healthy blood donors [106, 107]. *Bartonella* spp. could therefore be transmitted during transfusion [106, 107].

2. *Tropheryma whipplei* in asymptomatic carriers

Whipple's disease was first considered a chronic digestive disease and was then considered an acute pneumonia or epidemic fever [108, 109, 110]. Although the typical presentation includes diarrhea, weight loss, abdominal pain, and arthralgia, *T. whipplei* asymptomatic carriage in middle-aged men remains intriguing [111]. Two per cent to 44% of the population carries the bacterium in stools without clinical symptoms, but the worldwide annual incidence of the disease is only estimated at 12 new cases [112]. Immunosuppression has been shown to promote the activation of the disease as reported by various authors, with almost 50% of patients presenting with *T. whipplei* infection treated with immunosuppressive therapy before Whipple's disease diagnosis [113, 114, 115]. Genetic background, corticosteroids, and tumor necrosis factor inhibitors (10%) lead to a more rapid clinical progression and a clear onset [115, 116].

V. What is the rationale for treatment?

The international scientific community only recommends antibiotic treatment for two latent infections: latent syphilis and latent tuberculosis infection.

1. Treatment of latent syphilis to prevent late relapse and complications

Regarding the dramatic consequences of tertiary syphilis and the resurgence of congenital syphilis in developped countries, the Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO) both recommend treating this latent infection (Table 2) [117, 118].

2. Treatment of latent tuberculosis infection to prevent relapses in high priority groups

Patients with positive TST or positive interferon-gamma assay should undergo medical evaluation to rule out active tuberculosis. When active tuberculosis has been ruled out, the CDC and WHO recommend initiating an antibiotic therapy in patients belonging to high priority groups (Table 2) [119].

3. No evidence of antibiotic efficacy on subjective symptoms

a) Q fever chronic fatigue

Some studies have supported a biopsychological etiology for Q fever syndrome [8]. Although the benefits of the antibiotic therapy were controversially reported in the literature, a randomized study recently concluded on the issue. Cognitive behavioral therapy was effective in reducing fatigue severity in Q fever syndrome patients whereas prolonged therapy with doxycycline was not [6].

b) PTLDS

On the basis of the heterogeneous accuracy of serological testing for Lyme disease and the variety of subjective symptoms wrongly attributed to Lyme disease, no antibiotic treatment should be proposed in the absence of active infection confirmation (positive microbiological test and detection of an organic lesion).

In addition, a recent study performed by Goodlet *et al.* reported that oral or intravenous antibiotic therapies in cases of post-treatment Lyme disease symptoms were associated with an increased morbidity within 90 days [22].

Conclusion

Post-infectious chronic fatigue syndrome is characterized by subjective symptoms without evidence of living bacteria as the disease is not associated with relapses. Conversely, latent infection could be defined as an asymptomatic disease prone to reactivation in which the microorganisms are likely to be dormant. Furthermore, asymptomatic carriage is not associated by definition with subjective symptoms.

The subjective symptoms described in post-bacterial infection chronic fatigue syndrome are still misunderstood and no evidence is currently available to demonstrate that such symptoms could be related to a dormant bacterial infection or to carriage of viable bacteria. Other etiologies including psychological trauma may be part of these subjective symptoms. Post-infectious chronic fatigue syndrome could nonetheless be due to yet unknown microorganisms.

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Table 1. Evidence of bacterial survival without clinical symptoms in humans
Tableau 1. Données démontrant la survie bactérienne sans symptôme clinique chez l'homme

Bacteria	**Presentations**	**Site of latency**	**Cells**	**Factor favoring reactivation**
Bartonella henselae	Asymptomatic bacteremia	Blood, endothelium	Erythrocytes Endothelial cells	Immunosuppression
Tropheryma whipplei	Asymptomatic carriers	Unknown	Macrophages	Immunosuppression
Treponema pallidum	Recurrence in the secondary and tertiary stages	Lymph nodes Central nervous system	Unknown	Immunosuppression Congenital syphilis
Borrelia burgdorferi	Recurrence in the secondary and tertiary stages	Unknown	Unknown	None
Mycobacterium tuberculosis	Latent tuberculosis Recurrence	Granuloma	Macrophages Pneumocytes Fibroblasts Endothelial cells Adipocytes	Immunosuppression
Coxiella burnetii	Recurrence	Placenta Lymph nodes Bone marrow	Macrophages	Immunosuppression Pregnancy
Staphylococcus aureus	Recurrence	Blood Bone Joint Catheter Heart Respiratory tract	Epithelial cells Endothelial cells Fibroblasts Keratinocytes Osteoblasts	Unknown
Brucella abortus	None	Unknown	Unknown	Unknown
Rickettsia prowazekii	Brill-Zinsser recurrence	Lymph nodes	Endothelial cells	Unknown

Table 2. Treatment recommendation for latent infection in adults
Tableau 2. Recommandations thérapeutiques en cas d'infection latente chez l'adulte

Infection	**CDC recommendations**	**Treatment**
Latent *M. tuberculosis* infection	People with a positive IGRA result or a TST reaction of 5 or more millimeters • HIV-infected persons • Recent contacts of a TB case • Persons with fibrotic changes on chest radiograph consistent with old TB • Organ transplant recipients • Persons who are immunosuppressed for other reasons (e.g., taking the equivalent of >15 mg/day of prednisone for 1 month or longer, taking TNF-α antagonists) People with a positive IGRA result or a TST reaction of 10 or more millimeters • Persons from high-prevalence countries • Injection drug users • Residents and employees of high-risk congregate settings (e.g., correctional facilities, nursing homes, homeless shelters, hospitals, and other health care facilities) • Mycobacteriology laboratory personnel • Children under 4 years of age, or children and adolescents exposed to adults in high-risk categories	Isoniazid daily or twice weekly for 9 months Isoniazid plus rifapentine once weekly for 12 weeks Rifampin (or rifabutin) daily for 4 months
Latent *Treponema pallidum* infection	Latent syphilis is defined as syphilis characterized by seroreactivity without other evidence of primary, secondary, or tertiary disease. • Early latent syphilis: during the year preceding the diagnosis, they had 1) a documented seroconversion or a sustained (>2 week) fourfold or greater increase in nontreponemal test titers; 2) unequivocal symptoms of primary or secondary syphilis; or 3) a sex partner documented to have primary, secondary, or early latent syphilis. In addition, for persons with reactive nontreponemal and treponemal tests whose only possible exposure occurred during the previous 12 months, early latent syphilis can be assumed.	***Early latent syphilis*** Benzathine penicillin G 2.4 million units IM in a single dose ***Late latent syphilis or latent syphilis of unknown duration*** Benzathine penicillin G 7.2 million units total, administered as 3 doses of 2.4 million units IM each at 1-week intervals

	• Late latent syphilis or latent syphilis of unknown duration In the absence of these conditions, an asymptomatic person should be considered to have latent syphilis.	

IGRA: inter feron-gamma release assays; TST: tuberculin skin test; HIV: human immunodeficiency virus; TB: tuberculosis; TNF: tumor necrosis factor.