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# 1           **Characteristics and clinical outcomes after treatment of a national cohort of PCR-** 2   **positive Lyme arthritis**

3

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37

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54 **Abstract**

55 Objectives: To describe the clinical and microbiological characteristics and outcomes after  
56 antibiotic treatment of a national cohort of patients with Lyme arthritis confirmed by PCR  
57 testing on synovial fluid and by serology, when available.

58 Methods: Using the French National Reference Center for *Borrelia* database, patients with a  
59 positive PCR on synovial fluid for *Borrelia* were identified. Patient clinical and biological  
60 characteristics were reviewed from patient records. Long-term outcomes after treatment were  
61 studied through a questionnaire and with follow-up data.

62 Results: Among 357 synovial fluid testing by PCR between 2010 and 2016, 37 (10.4%) were  
63 positive for *Borrelia*. Patients' median age was 36 years (range 6-78) with 61% of men and  
64 28% patients under 18. The presentation was monoarticular in 92% and the knee was  
65 involved in 97%. Contrary to the *Borrelia* species repartition in European ticks,  
66 *B. burgdorferi* sensu stricto was the most prevalent species found in synovial fluid (54%)  
67 followed by *B. azfeli* (29%) and *B. garinii* (17%). Antibiotic treatments were mainly  
68 composed of doxycycline (n=24), ceftriaxone (n=10) and amoxicillin (n=6), for a median  
69 duration of 4 weeks (range 3-12). Despite a properly conducted treatment, 34% of patients  
70 (n=12) developed persistent synovitis for at least 2 months (median duration 3 months, range  
71 2-16). Among those, 3 developed systemic inflammatory oligo- or polyarthritis in previously  
72 unaffected joints with no signs of persistent infection (repeated PCR testing negative), which  
73 mandated Disease-Modifying Antirheumatic Drugs (DMARD) introduction, leading to  
74 remission.

75 Conclusion: In France and contrary to ticks ecology, Lyme arthritis is mainly caused by  
76 *B. burgdorferi* sensu stricto. Despite proper antibiotic therapy, roughly one third of patients  
77 may present persistent inflammatory synovitis and a small proportion may develop systemic  
78 arthritis. In such cases, complete remission can be reached using DMARD.

79 Key messages :

- 80 - Contrary to tick ecology (with *B. afzelii* being the most frequent species) ,
- 81 *B. burgdorferi* sensu stricto is the most common species involved in Lyme arthritis in
- 82 France.
- 83 - After one run of proper antibiotic therapy, roughly one third of patient develop
- 84 persistent inflammatory synovitis.
- 85 - Nearly 10% of patients developed systemic arthritis with negative repeat PCR test and
- 86 good DMARD response.

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88

## 89 **Introduction**

90 Lyme borreliosis (LB) is the most common vector-borne disease in the Northern  
91 Hemisphere.(1) The spirochete bacteria causing LB, *Borrelia burgdorferi* sensu lato complex,  
92 are transmitted by hard ticks belonging to the genus *Ixodes*.(2) In Europe, the most three  
93 frequent species responsible for human infections are *B. afzelii*, *B. garinii* and *B. burgdorferi*  
94 sensu stricto, whereas *B. burgdorferi* sensu stricto is almost the only species causing LB in  
95 North America.(3) In Europe, neuroborreliosis is the most frequent disseminated clinical  
96 manifestation of LB, followed by Lyme arthritis, acrodermatitis chronica atrophicans, and,  
97 more rarely, borreliolymphocytoma, and Lyme carditis.(4–6) These different clinical  
98 pictures are linked to the great species diversity found in Europe. Conversely, in the US,  
99 Lyme arthritis (LA) is the most common feature of disseminated LB, and as *B. burgdorferi*  
100 sensu stricto is the main species found in the US it has been hypothesized that it is the main  
101 etiologic agent for LA in the US and in Europe.

102 The clinical manifestations of LA, include synovitis, usually in one or a few large  
103 joints, especially the knee.(7) For untreated cases, recurrent joint-swelling episodes may

104 persist for months or even years. The diagnosis of LA can be challenging, especially in high  
105 endemic areas, and cannot be based on a single clinical or biological characteristic. High  
106 levels of IgG antibodies against *Borrelia* are found in serum from patients with LA, but  
107 although serological testing shows excellent sensitivity and specificity in LA, a positive result  
108 alone is not sufficient to make the diagnosis.(8) The bacterial culture in LA is ineffective,  
109 because of its weak sensitivity.(8) Molecular diagnosis on the synovial fluid using PCR  
110 detecting *Borrelia* DNA is an attractive add-on test in LA diagnostic algorithm, providing a  
111 100% specificity and a 42-96% sensitivity.(8–10)

112         The treatment of LA is based on antibiotics, generally for 3 to 4 weeks, and the vast  
113 majority of patients recover completely.(5,11) In the US, roughly 10% of patients develop  
114 persistent synovitis lasting  $\geq 2$  months, called slowly resolving or antibiotic-refractory LA.(7)  
115 Although slowly resolving LA pathophysiology remains obscure, there is strong evidence for  
116 an autoimmune or inflammatory mechanism,(12–15) and little to none for persistent infection.

117         Since few data about clinical and microbiological features and outcome of patients  
118 with LA are available in Europe, we conducted a retrospective observational study to describe  
119 the clinical and biological characteristics and treatment outcomes of a national cohort of  
120 patients with LA confirmed with synovial fluid PCR.

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129 **Patients and Methods**

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131 **Patients**

132 We conducted a retrospective observational study using the French National Reference  
133 Centre (NRC) for *Borrelia* database. Among its missions, the French NRC for *Borrelia*  
134 contributes to the epidemiological surveillance of LB. Between 2010 and 2016 all the patients  
135 referred to the NRC for *Borrelia* PCR testing and who had a positive *Borrelia* PCR (n=37) in  
136 their synovial fluids were included. Patients' medical history and laboratory findings, when  
137 available, were reviewed from medical records (Figure 1). Time to diagnosis was calculated  
138 as the time between the first reported articular symptoms (retrieved from the medical report)  
139 and the PCR testing. The duration and route of antibiotic therapy were retrieved from medical  
140 records. In order to study treatment outcome, patients were submitted a standardized  
141 questionnaire by their referent physician. This questionnaire included reported articular or  
142 other sequelae, asthenia or reported invalidity. Follow-up clinical data were also retrieved  
143 from their referent physician.

144

145 ***Borrelia* ELISA and western-blot**

146 *Borrelia* ELISA were realized using different commercial kits done by the considered  
147 hospital taking care of the patients (Euroimmun Lyme ELISA IgG IgM, Diasorin Liaison  
148 XL® *Borrelia* IgG IgM, Biomérieux Vidas® Lyme panel, Siemens Enzygnost® IgG IgM,  
149 Mikrogen recomwell® *Borrelia* IgG IgM).

150 Serum *Borrelia* western-blot using different commercial kits (Biosynex LYMECHECK®  
151 Optima IgG IgM, Mikrogen *recomLine*® *Borrelia* IgG IgM, Euroimmun Euroline® *Borrelia*-  
152 RN-AT-Adv) or an in-house test as previously described.(17)

153

154 ***Borrelia* polymerase chain reaction testing**

155 *Borrelia* PCR in synovial fluid were conducted as previously described.(18). Briefly,  
156 presence or absence of *Borrelia* DNA was assessed by a specific real-time PCR assay  
157 targeting a 230 bp DNA fragment from the conserved region of the flagellin (*fla*) gene of  
158 the *Borrelia burgdorferi sensu lato* complex and a Taqman® probe (11 bp). Then *Borrelia*  
159 species identification was realized by a second real-time DNA amplification using  
160 hybridization probes targeting species-specific regions of the *fla* gene for *B. afzelii*, *B.*  
161 *garnii*/*B. bavariensis*, *B. burgdorferi* ss, *B. bissettii*, *B. valaisiana* and *B. lusitaniae*. All PCR  
162 tests were performed in the same laboratory (*Borrelia* NRC located in Strasbourg, France).

163

164 **Statistical analyses**

165 Data were analysed using GraphPad Prism Version 6.03. Non-parametric Kruskal-  
166 Wallis test followed by a Dunn's correction for multiple testing was used to compare the  
167 distribution of numerical variables. Mann-Whitney test was used when Kruskal-Wallis test  
168 was not applicable. Unadjusted associations between serum CRP levels and synovial fluid  
169 leucocytes count were estimated with Spearman correlation coefficient. Fisher's exact tests  
170 were used to compare categorical variables. P values (bilateral) <0.05 were considered  
171 statistically significant.

172

173 **Ethical considerations**

174 This study was approved by the Ethic Committee of the Faculty of Medicine and  
175 Strasbourg University Hospital, with the reference number 2018-4.

176

177



178 **Results**

179

180 **Patient characteristics**

181           Between 2010 and 2016, 357 synovial fluids (SF) were tested by the French National  
182 reference centre. *Borrelia* DNA was detected in 37 (10.4%) of them (Figure 1). Positive  
183 samples came from many regions of France where LB has been previously reported  
184 (Figure 2)(19). Patient characteristics are summarized in Table 1. Median time to diagnosis  
185 was 3 months (range 1-112 months) after clinical symptoms onset, and was significantly  
186 longer in adults than children (4 vs 1.5 months, respectively,  $p=0.03$ ). On a seasonal point of  
187 view, date of the first clinical signs was observed during winter for 11 patients, spring for  
188 6 patients, summer for 10 patients and fall for 8 patients (without significant difference). No  
189 significant differences were observed between diagnosis delay and *Borrelia* species, or  
190 between patients' age and *Borrelia* species.

191

192 **Clinical presentation at diagnosis**

193           The presentation was monoarticular in 92% (34/37) cases, and oligoarticular in the  
194 other cases. The knee was involved in 97% (36/37) patients, other involved joints were the  
195 ankle ( $n = 1$ ) and the elbow ( $n = 1$ ). Fever ( $>38^{\circ}\text{C}$ ) was reported in 22% (8/37) patients and  
196 was significantly more frequent in patients under 18 years old (45.5% vs 11.5%,  $p = 0.035$ ).  
197 Erythema migrans was reported by 14% (6/33) of patients. Other manifestations included  
198 headaches ( $n = 2$ ), cervico-brachial neuralgia ( $n = 1$ ), leukocytoclastic vasculitis ( $n = 1$ ). None  
199 of the patients was diagnosed with concomitant cardiac Lyme disease manifestation. The  
200 characteristics are detailed in Table 1.

201

202

## 203 **Laboratory Findings**

204 Lyme borreliosis serology was available for 33 patients, who all had IgG antibodies  
205 against *Borrelia* with the ELISA assay (Table 1). Western-blot were positive with the  
206 presence of at least 5 specific bands in 97% (32/33) of our cohort. One patient had a non-  
207 significant western-blot result with only 3 bands detected (41, 50 and 83 kDa bands). This  
208 patient had a 6-month diagnosis delay. Forty percent (12/30) of patients had detectable IgM  
209 antibodies against *Borrelia*. No association was observed between IgM positivity and  
210 *Borrelia* species, patients' age, or diagnosis delay or resolution of symptoms (data not  
211 shown).

212 Among available synovial fluid counts (n = 18), the median SF count was 25000 (range 1400  
213 – 300000) with a median neutrophil percentage of 90% (range 65-99). C-reactive protein  
214 (CRP) level was high (> 5mg/L) in 91% of patients, with a median value of 45 mg/L (range 3-  
215 182). CRP level was associated with leucocytes count in synovial fluids ( $r^2$ : 0.423; p = 0.003).

216 Among the 37 patients with a positive *Borrelia* PCR in SF, PCR detected  
217 *B. burgdorferi* sensu stricto DNA in 19 patients (54%), *B. afzelii* DNA in 10 patients (29%),  
218 and *B. garinii* DNA in 6 patients (17%) (Figure 3). No statistical difference was observed in  
219 the annual species repartition or in the annual ratio of positive samples on total samples  
220 tested. Most of the molecular analyses were performed on synovial fluids obtained from  
221 patients who hailed from the North of France.

222

## 223 **Treatment**

224 Antibiotic treatments used were oral doxycycline (n = 24), intravenous ceftriaxone  
225 (n = 10), oral amoxicillin (n = 6), oral tetracycline (n = 1) and oral cefaclor (n = 1). Five  
226 patients received a combination therapy (doxycycline and ceftriaxone). Three of them  
227 received ceftriaxone after doxycycline, one received doxycycline after 4 days of ceftriaxone

228 and one received both at the same time. Ceftriaxone therapy was added when inadequate  
229 response to oral therapy was observed. Median antibiotic treatment duration was 4 weeks  
230 (range 3 to 12). After the diagnosis, 9 patients received intra-articular glucocorticoids  
231 including 8 patients who had antibiotic-resistant LA. Seven received triamcinolone  
232 hexacetonide synoviorthesis, as initial treatment for the arthritis (n = 1) or as adjunctive  
233 treatment for persistent synovitis (n = 6). One patient received isotopic synoviorthesis  
234 (detailed in next paragraph). None of them had to undergo surgical synovectomy.

235

### 236 **Clinical outcome after treatment**

237 Follow-up data after treatment were available for 35 (95%) patients with a median  
238 follow-up time of 17 (range 1-73) months (Figure 1). Sixty-six percent of patients (n = 23)  
239 had a rapid resolution of the arthritis whereas 34% (n = 12) presented residual synovitis  
240 lasting  $\geq 2$  months after oral antibiotic or 1 month after IV antibiotic (also called antibiotic  
241 refractory LA).

242 Among the 23 patients with rapid resolution of the arthritis, 78% (n = 18) presented a full  
243 recovery and 22% (n = 5) reported long-lasting residual mechanical pain in the affected joint.  
244 The residual mechanical pain was moderate and did not significantly limit the patients'  
245 activities.

246 Among the 12 patients with residual clinical synovitis lasting  $\geq 2$  months (median  
247 duration 3 months, range 2-16) after one course of oral antibiotic treatment or for at least  
248 1 month after IV treatment, *Borrelia* PCR testing in SF was repeated in 9 patients, and all  
249 tests were negative. Three of them received combination treatment with doxycycline and IV  
250 ceftriaxone. The initial treatment of the residual synovitis consisted of non-steroidal anti-  
251 inflammatory drugs and intra-articular glucocorticoid injections were used in 75% cases. Half  
252 (n = 6) of these patients with residual synovitis presented a full recovery, 17% (n = 2)

253 reported long-lasting residual mechanical pain in the affected joint, 25% (n=3) developed  
254 systemic inflammatory arthritis in initially non-affected joints (Figure 1). One patient with  
255 persistent knee synovitis despite doxycycline (4 weeks) and IV ceftriaxone (3 weeks)  
256 underwent isotopic synoviorthesis (intra-articular injection of a radioactive isotope (i.e.  
257 <sup>90</sup>Yttrium) to decrease synovial inflammation). The isotopic synoviorthesis was performed  
258 after persistent *Borrelia* infection was ruled out by repeat synovial fluid PCR and after a  
259 relapse despite triamcinolone hexacetonide synoviorthesis and 3 months treatment with oral  
260 methotrexate (15mg/week). He did not present subsequent articular flare-up. One patient with  
261 negative repeat synovial fluid PCR developed symptoms suggestive of chronic pain syndrome  
262 without inflammatory joint disease. Characteristics of patients with or without slowly  
263 resolving synovitis are presented in Table 2.

264         The characteristics of the 3 patients who developed diffuse inflammatory arthritis are  
265 detailed in Table 3. Briefly, the 3 patients presented oligo- or polyarthritis involving  
266 previously non-affected joints. One patient developed dactylitis, no patient developed axial or  
267 extra-articular involvement. *Borrelia* PCR testing on SF was repeated for all these 3 patients,  
268 with negative results. Laboratory testing for autoimmunity (including at least antinuclear  
269 antibody and ACPA) was negative for all the 3 patients. None of these 3 patients had HLA-  
270 DR locus typed. All these 3 patients were started on methotrexate at an oral dose of 15 to  
271 20mg/week leading to sustained remission in 2 patients. Adalimumab was added to the third  
272 patient's treatment regimen, leading to sustained remission.

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278 **Discussion**

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280 To determine clinical and biological characteristics and treatment outcome of patients  
281 with proven Lyme arthritis, we examined data from 37 patients with a positive *Borrelia* PCR  
282 on synovial fluid.

283 The diagnosis of LA is currently based on the presence of specific symptoms,  
284 combined with laboratory evidence for infection. Serology is the cornerstone of Lyme disease  
285 laboratory diagnosis, and serological tests that are most often used are enzyme-linked  
286 immuno-sorbent assays (ELISAs) followed by immunoblots. In our cohort, all patients with  
287 available serological data (33/33) showed a positive ELISA IgG result. It is noteworthy that  
288 all *Borrelia* serology were sampled at the same time or after the synovial fluid and that PCR  
289 was performed independently of the serology. Therefore no bias of inclusion criteria related to  
290 the *Borrelia* serological result was possible in our cohort. In LA, serological tests such as  
291 ELISAs IgG are known to show a great sensitivity (93-100%) and specificity (91-97%) (20).  
292 ELISAs IgM are known to be less sensitive than IgG in LA, and their presence was found in  
293 only 40% cases of our cohort. Thus, positive *Borrelia* IgG with negative IgM should not be  
294 considered as a “serological scar” and discard the diagnosis.

295 In our study, the diagnosis of LA was always confirmed by a positive SF PCR for *Borrelia*.  
296 Molecular diagnosis on the synovial fluid using PCR detecting *Borrelia* DNA is an interesting  
297 add-on diagnostic tool in LA diagnosis. In Europe, its sensibility is roughly 60-70% (8–10)  
298 and a PCR positivity in synovial fluid, in case of positive serology allows diagnosis certainty  
299 (100% specificity), which is not the case with serology alone. In a practical point of view,  
300 molecular diagnosis must be realized when serological tests are positive. Several points  
301 support this conception: On the one hand, some patients with LA will have a negative  
302 *Borrelia* PCR test in their synovial fluid, which can be due to low spirochaetal load, technical

303 failure of the PCR or DNA degradation due to incorrect pre-analytic sample handling. On the  
304 second hand, since virtually all patients described in the literature as having LA have a  
305 positive serology, serology should be realized first considering its lower cost and that a false  
306 positive results due to external contamination is at least theoretically always possible. If PCR  
307 testing is negative (and serology is positive), differential diagnoses should be considered, but  
308 LA diagnosis remains still possible.

309 In comparison with serology, repeat PCR test turns negative after antibiotic treatment,  
310 sometime with a few months delay.(16) In one American study, spirochaetal DNA could be  
311 found in some patients after antibiotic therapy, however, amplification of mRNA (marker of  
312 spirochaetal viability) was negative in all patients, suggesting dead bacteria remnants rather  
313 than persistent infection. (16) In our study, all synovial fluid PCR repeated after antibiotic  
314 treatment among whom 9 had antibiotic refractory LA, were negative (n =14).

315 In Europe, the most frequent species responsible for human LB are *B. afzelii*,  
316 *B. garinii* and *B. burgdorferi sensu stricto*, whereas the most frequent species that causes LB  
317 in North America is mainly *B. burgdorferi sensu stricto*.(3) In France and all over Europe,  
318 *B. burgdorferi sensu stricto* is the least frequent species found in the *Ixodes ricinus*, the main  
319 vector of LB in Europe. In a recent meta-analysis, the major *Borrelia* species found in  
320 European *I. ricinus* ticks was *B. afzelii* (46.6%), followed by *B. garinii* (23.8%), then  
321 *B. burgdorferi sensu stricto*, found in only 10.2% of ticks.(21) In European patients with LB,  
322 EM is the most frequent clinical manifestation, and is mainly associated with *B. afzelii*;(22–  
323 24) the second most frequent clinical picture is neuroborreliosis and is mainly associated with  
324 *B. garinii*.(25) Interestingly, the most frequent *Borrelia* species found in synovial fluids from  
325 our patients was *B. burgdorferi sensu stricto* (54%). A potential bias could be that PCR  
326 technique may have different sensibility, meaning that some organisms are more likely to be  
327 identified than others. But our PCR technique is routinely used and sensitivity is the same for

328 all *Borrelia* strains. For example, in erythema migrans biopsies, *B. afzelii* is found in more  
329 than 90% of cases (personal communication). Our observations are concordant with some  
330 other previous studies, in which *B. burgdorferi* sensu stricto was found to be more frequent  
331 than the other species in European LA.(26,27) However, some studies did not observe this  
332 correlation.(28,29) In Europe, *Borrelia* strains causing Lyme arthritis are greatly  
333 heterogeneous, and our study, based on French data, might not be extrapolated to other  
334 European countries. Although our study provides the largest cohort of European LA patient  
335 with *Borrelia* species determination, a global survey involving other European countries may  
336 help to elucidate this question.

337 Initial clinical presentations in our LA cohort were classical, with joint swelling of a  
338 large articulation (especially the knee, in 97%), as previously reported in a cohort of 65 US  
339 patients with LA.(30) Fever was rarely reported but significantly associated with children  
340 borreliosis which are known to experience a more acute presentation.(31) These observations  
341 occurred from weeks to months after a tick bite, although only 40% of patients remembered  
342 this bite. In a European case series, the period from tick bites or EM to the onset of LA ranged  
343 from 10 days to 16 months.(32) Because of this great variability of the latency period, there is  
344 no seasonal peak in the occurrence of LA.(30) We also observed this characteristic in our  
345 cohort, since the date of the first clinical signs was observed all over the year. History of a  
346 prior EM to LA is a rare phenomenon. Herein, only 6 (16.2%) of our 37 patients remembered  
347 an EM before LA presentation. Based on European studies, history of EM in case of LA is  
348 ranged between 10 to 32%.(33–35)

349 Diagnosis delay was usually short, with 18/35 patients diagnosed between 1 and  
350 3 months after clinical signs appearance ; 4/35 patients were diagnosed after 12 months, with  
351 one patient after 112 months. This shows that LA is sometimes a difficult diagnosis, and

352 should be systematically investigated for in the presence of a monoarticular or oligoarticular  
353 arthritis with negative culture and crystal observation, especially in case of knee involvement.

354 Antibiotic course mostly included doxycycline, ceftriaxone or amoxicillin for a  
355 median time of 4 weeks. All these treatment regimen have a proven efficacy in LA (35,36). In  
356 our study, one third of patients presented persistent synovitis lasting at least 2 months after a  
357 well-conducted oral antibiotic treatment or 1 month after IV treatment. This condition is  
358 called slowly resolving or antibiotic-refractory Lyme arthritis in the literature and is usually  
359 reported in roughly 10% of patients in US cohorts and thought to be even rarer in Europe  
360 (38,39). Although its pathophysiology remains unclear, the current preferred paradigm is an  
361 autoimmune reaction against *Borrelia* antigens or a loss of tolerance against an unidentified  
362 autoantigen rather than persistent *Borrelia* infection (38). In line with this paradigm, all  
363 9 repeated synovial fluid PCR testing in our patients with antibiotic-refractory LA were  
364 negative. Interestingly, matrix metalloprotease 10, an auto-antigen targeted by B and T  
365 lymphocytes, have been identified in some patients with antibiotic-refractory LA, reinforcing  
366 the autoimmune hypothesis.(40) Association between antibiotic-refractory LA and certain  
367 HLA-DR haplotype has been reported.(12) Unfortunately, HLA-phenotyping could not be  
368 performed in our study. Our data suggest that slowly resolving LA is not uncommon in  
369 Western Europe or at least in France. Clinical outcomes were favourable for 67% with  
370 symptomatic treatments (NSAID or intra-articular glucocorticoids). One patient with slowly  
371 resolving LA with negative follow-up PCR testing later developed symptoms suggestive of  
372 chronic pain syndrome. Finally, 3 patients (25% of patients with persistent synovitis and 9%  
373 from our follow-up cohort) developed systemic arthritis after antibiotic treatment. Systemic  
374 arthritis is a poorly identified complication of LA which incidence and pathogenesis are  
375 largely unknown. Infection-induced rheumatic disease (eg, rheumatoid arthritis) or post-  
376 spirochaetal reactive polyarthritis are two viable hypothesis but further fundamental work is



377 needed. A recent report described 30 rheumatoid arthritis-like and psoriatic arthritis-like cases  
378 following LA diagnosis in the US.(41) One critic voiced by Tuttle was that LA diagnosis was  
379 based on serology alone and that testing to investigate for persistent *Borrelia* infection in  
380 these patients was not reported. (42) However, in the 5 patients in whom synovial fluid was  
381 available, testing for *Borrelia* DNA was negative, which supports the conclusion that these  
382 patients did not have persistent *Borrelia* infection. In our study, the facts that all 3 patients  
383 developing systemic arthritis had negative repeated SF *Borrelia* PCR testing and an excellent  
384 response to DMARD treatment strongly argue against persistent infection.

385         One of the strengths of our study is the direct involvement of the French national  
386 reference centre for *Borrelia*. The French national reference centre for *Borrelia* based in  
387 Strasbourg since 2012 provides diagnosis testing for all regions of France thus allowing a  
388 representative capture of French PCR-positive LA cases. Besides, since patients' inclusion  
389 was based on synovial fluid PCR positivity, the LA diagnosis was proven in all cases. The  
390 main limit of our study is that due to the retrospective analysis, some data were not available  
391 for analysis. Two patients (5% of the cohort) could not be contacted in order to study the after  
392 treatment outcome. Another limitation is that due to the multicentre origin of our cohort, we  
393 were not able to reunite a cohort of LA with a negative PCR for use as a control group.  
394 However, the main aims of our study were to describe clinical characteristics and treatment  
395 outcome of PCR-proven LA, for which a control group was deemed unnecessary. Besides, as  
396 a positive serological test alone does not mean that a patient necessarily has active Lyme  
397 borreliosis, the additive value of this type of control group may be not relevant.

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399         In conclusion we report 37 cases of synovial fluid PCR-positive Lyme arthritis in  
400 French patients. We identify *B. burgdorferi* sensu stricto as the main species involved in LA,  
401 in spite of its low prevalence in European ticks. After antibiotic treatment, follow-up

402 identified 34% (12/35) patients with slowly resolving arthritis among whom 25% (3 patients,  
403 9% of the follow-up cohort) developed systemic inflammatory arthritis without any sign of  
404 persistent infection (negative repeat PCR testing). Our study suggests that European patients  
405 with LA may present post-infectious inflammatory manifestation in a significant proportion  
406 of cases.

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411 Lyme arthritis, and Marie-Christine Michellet for English revision.

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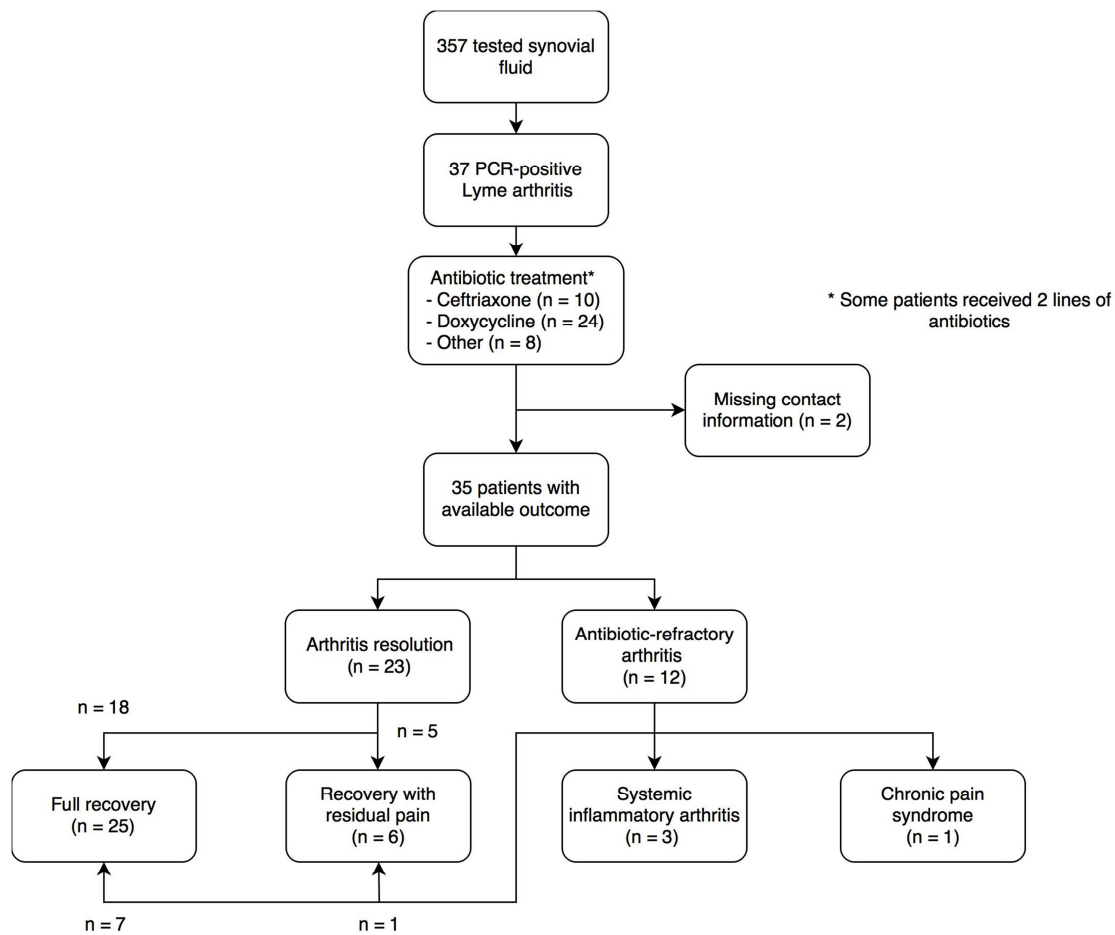
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552 **Figures**

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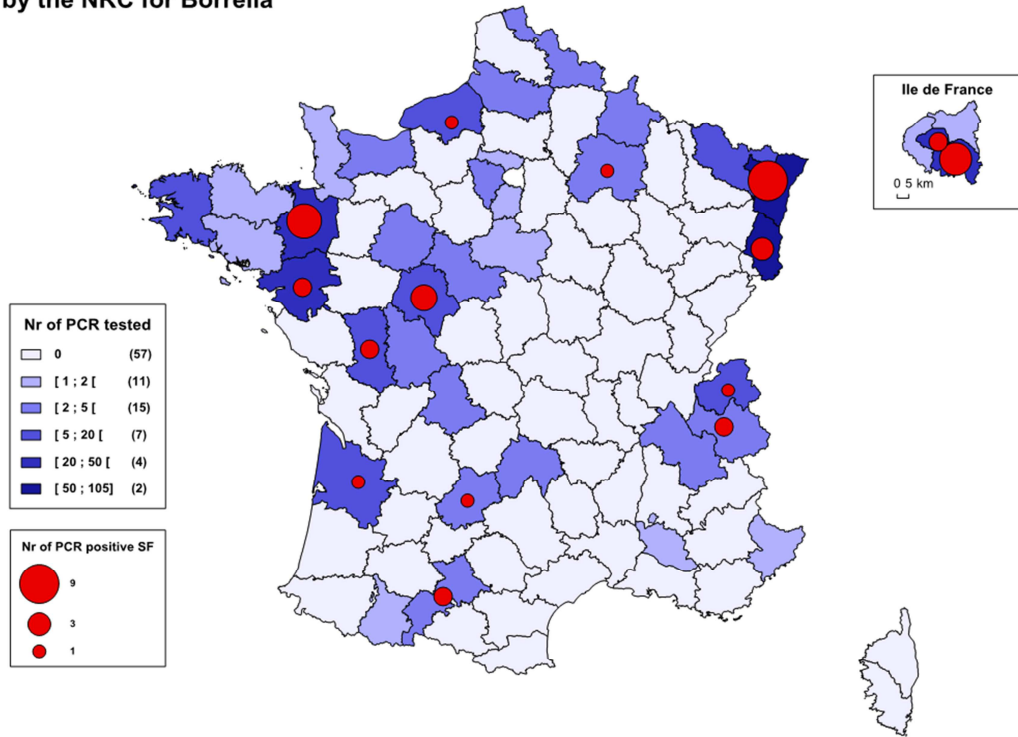


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555 Figure 1. Included patients' flowchart through the study. From our database of 357 tested  
 556 synovial fluids from 2010 to 2016, 37 were positive for *Borrelia* DNA. Of these 37 patients,  
 557 35 had available follow-up data after treatment. Twenty-three patients had rapid resolution of  
 558 the arthritis whereas 12 presented residual synovitis lasting  $\geq 2$  months. Among the  
 559 23 patients with rapid resolution of the arthritis, 18 presented a full recovery and 5 reported  
 560 residual mechanical pain in the affected joint. Among the 12 patients with residual synovitis,  
 561 6 patients presented a full recovery, 2 reported residual mechanical pain in the affected joint,  
 562 3 developed systemic inflammatory arthritis in initially non-affected joints and 1 showed  
 563 symptoms suggesting chronic pain syndrome.



Geographical repartition of the PCR tested/PCR positive SF during the 2010-2016 period by the NRC for Borrelia



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566 Figure 2. Geographical distribution of synovial fluids tested by PCR and positive results for

567 *Borrelia* DNA in the French National Reference Centre for *Borrelia* from 2010 to 2016.

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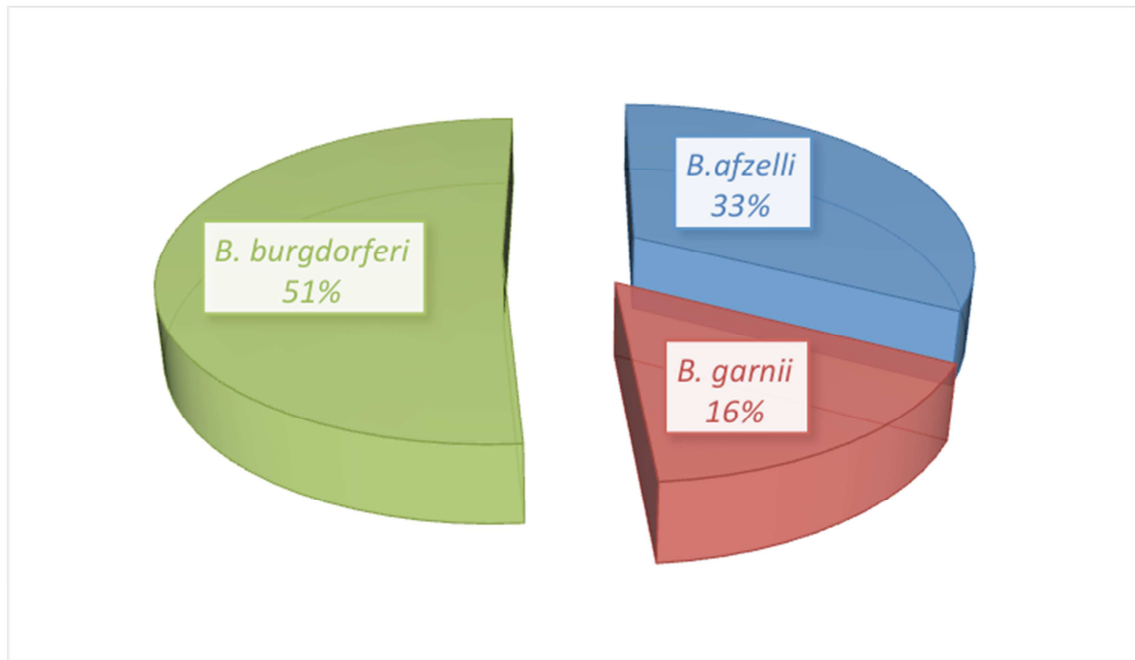
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579 Figure 3. Repartition of *Borrelia* species found in synovial fluids from 2010 to 2016.

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594 Table 1: Patient, disease and treatment characteristics at diagnosis

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Characteristics at diagnosis	PCR-positive Lyme Arthritis (n = 37)
<b>Patient characteristics</b>	
Age, median (range), years	36 (6 - 78)
Minor < 18 years	28% (11/37)
Male Sex	61% (23/37)
Tick exposure	91% (29/32)
History of tick bite	45% (15/33)
Diagnostic delay, median (range), months	3 (1 - 112)
<b>Clinical presentation</b>	
Previous erythema migrans	19% (6/32)
Monoarthritis	92% (34/37)
Oligoarthritis	8% (3/37)
Knee involvement	97% (36/37)
Fever (>38°C)	22% (8/37)
<b>Laboratory findings</b>	
C-reactive protein, median (range), mg/L	45 (3-182)
Positive <i>Borrelia</i> serology (ELISA)	100% (37/37)
Positive <i>Borrelia</i> western-blot	97% (36/37)
Negative <i>Borrelia</i> western-blot	3% (1/37)
Joint fluid aspiration	
leukocyte count > 2000/mm <sup>3</sup>	95% (18/19)
Leukocyte count, median (range)	25000 (1400 - 300 000)
% of neutrophils, mean (SD)	85% (±10%)
<b>Antibiotic regimen</b>	
Treatment duration, median (range), weeks	4 (3 - 12)
Doxycycline	65% (24/37)
Ceftriaxone	27% (10/37)
Amoxicillin	16% (6/37)
Other	5% (2/37)

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603 Table 2: Characteristics of patients with or without persistent arthritis

Characteristics at diagnosis	Arthritis resolution (n = 23)	Persistent arthritis (n = 12)	P-value
<b>Patient characteristics</b>			
Age, median (range), years	33 (6-75)	41 (12-78)	0.48
Minor < 18 years	39% (9)	17% (2)	0.26
Male Sex	65% (15)	28% (7)	0.73
Diagnostic delay, median (range), months	3 (1-112)	5 (1-24)	0.27
<b>Clinical presentation</b>			
Monoarthritis	96% (22)	83% (10)	0.27
Oligoarthritis	4% (1)	17% (2)	0.27
Fever	26% (6)	17% (2)	0.69
<b>Laboratory findings</b>			
C-reactive protein, median (range), mg/L	37 (3-182)	61 (6-136)	0.46
Synovial fluid aspiration			
Leukocyte count, median (range)	17000 (1400-300000)	27000 (2700-60000)	0.31
<i>Borrelia</i> species			0.64
<i>B. burgdorferi</i> sensu stricto	48% (11)	67% (8)	
<i>B. afzelii</i>	30% (7)	25% (3)	
<i>B. garinii</i>	22% (5)	8% (1)	
<b>Antibiotic regimen</b>			
Treatment duration, median (range), weeks	4 (3-12)	6 (3-12)	0.09
Doxycycline	57% (13)	83% (10)	0.15
Ceftriaxone	22% (5)	33% (4)	0.69
Amoxicillin	22% (5)	8% (1)	0.64
Other	9% (2)	0%	0.53

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614 **Table 3. Characteristic of patients developing chronic systemic arthritis.**

Characteristics at diagnosis	Patient 1	Patient 2	Patient 3
<b>Age</b>	24 years	28 years	14 years
<b>Sex</b>	Female	Male	Male
<b>Initial clinical presentation</b>	Acute knee monoarthritis No fever no EM	Acute right knee arthritis Left knee arthritis 4 weeks earlier No fever no EM	Acute left knee arthritis Right knee arthritis 6 weeks earlier Leukocytoclastic purpura No fever no EM
<b>CRP level</b>	3 mg/L	8mg/L	84mg/L
<b>SF leukocyte count</b>	2400/mm <sup>3</sup> 75% neutrophils	17600/mm <sup>3</sup> neutrophil count NA	25000/mm <sup>3</sup> 90% neutrophils
<b>Borrelia species</b>	<i>B. garinii</i>	<i>B. burgdorferi</i> sensu stricto	<i>B. azfeli</i>
<b>Initial treatments</b>	Tetracyclin 600mg/day 4 weeks Naproxen	<b>Before diagnosis :</b> Oral MTX 15mg/week Hexatrione acetone <b>At diagnosis :</b> Doxycycline 200mg/day 12 weeks MTX discontinuation	Doxycycline 200mg/day 8 weeks Naproxen
<b>Inflammatory disease presentation</b>	Asymmetric oligoarthritis: right knee and hip, left ankle	Knee bi-arthritis and dactylitis	Asymmetric polyarthritis: left wrist and elbow, right wrist and 2 <sup>nd</sup> MCP
<b>New SF PCR</b>	Negative	Negative	Negative
<b>Immune panel</b>	ANA and ACPA negative	ANA and RF and ACPA negative	ANA and ACPA negative
<b>B27 status</b>	Negative	NA	Negative
<b>Treatments</b>	MTX 15 mg/week	MTX 15mg/week Hexatrione acetone Adalimumab 40mg/2weeks	MTX 15mg/week
<b>Outcome</b>	Rapid remission MTX discontinuation after 24 months No recurrence at 3 months	Flare-up with MTX alone Remission with MTX+ADA Treatment still ongoing	Rapid remission MTX discontinuation after 18 months No recurrence at 1 year of follow-up

Lost of follow-up

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616 Abbreviations : ACPA, anti-citrulinated protein antibody; ANA, anti-nuclear antibody; CRP,  
617 C-reactive protein; ECM, erythema migrans; MTX, methotrexate; RF, rheumatoid factor; SF,  
618 synovial fluid; NA, not available

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