Review

Treatment of Lyme borreliosis

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Abstract

Borrelia burgdorferi sensu lato is the causative agent of Lyme borreliosis in humans. This inflammatory disease can affect the skin, the peripheral and central nervous system, the musculoskeletal and cardiovascular system and rarely the eyes. Early stages are directly associated with viable bacteria at the site of inflammation. The pathogen–host interaction is complex and has been elucidated only in part. *B. burgdorferi* is highly susceptible to antibiotic treatment and the majority of patients profit from this treatment. Some patients develop chronic persistent disease despite repeated antibiotics. Whether this is a sequel of pathogen persistence or a status of chronic auto-inflammation, auto-immunity or a form of fibromyalgia is highly debated. Since vaccination is not available, prevention of a tick bite or chemoprophylaxis is important. If the infection is manifest, then treatment strategies should target not only the pathogen by using antibiotics but also the chronic inflammation by using anti-inflammatory drugs.

Introduction

In recent decades much has been learned about the aetiology of *Borrelia burgdorferi* infection and the transmitting arthropod, the tick. The exact pathogenesis, however, especially of late-stage manifestations of Lyme disease, is far from clear. Several models of disease pathogenesis and the treatment options are being debated controversially. This debate is reflected in a significant uncertainty of how to treat long-term manifestations of the disease in particular. The authors of the present review have tried to summarise what is known about disease aetiology, pathogenesis and treatment from these different perspectives in order to provide a basis for future discussions.

Clinical disease and pathogenesis of Lyme disease

Borrelia species, the transmitting vectors and early skin manifestations

Lyme borreliosis in adults has been divided into three clinical stages [1,2]. The early manifestations of the infection mainly involve the skin and the nervous system. At the site of the tick bite an erythema migrans regularly develops, but can be absent in up to 20 to 50% of patients [3] depending on the region of the reports. The skin lesion is infrequently accompanied by unspecific symptoms of a systemic infection, including malaise, fatigue, headache, fever and regional lymphadenopathy.

In the USA, erythema migrans seems to be present more regularly than in Europe; it has been associated with a comparably more intense inflammation and a systemic spread of the pathogen, which might reflect that in the USA only one species of *B. burgdorferi* sensu lato – namely *B. burgdorferi* sensu strictu – is responsible, whereas in Europe further species – *Borrelia afzelii* and *Borrelia garinii*, and recently *Borrelia spielmanii* [4,5] – have been identified. Another early skin manifestation, *Borrelia* lymphocytoma (lymphadenosis cutis benigna) – a purple nodular lesion affecting the ear, the nose or the breast nipple – has only been reported in European patients [6]. This may again reflect the presence of different regional *Borrelia* genotypes and/or strains.

Despite these differences in aetiology, the clinical manifestations are otherwise quite comparable. A few weeks to months after the pathogen has been transferred from the vector, especially *Ixodes* ticks, to the human host, several organs may become affected, probably because of a haematogenous spread of the pathogen. The arthropod vector differs geographically. In Europe *Ixodes ricinus* is transmitting the pathogen, whereas in America the transmitting species is *Ixodes scapularis*.

Early dissemination of the pathogen

The next phase of disease is denominated early dissemination. A systemic disease evolving out of a single erythema

CNS = central nervous system; CSF = cerebrospinal fluid; Osp = outer surface protein; PCR = polymerase chain reaction.

migrans lesion has been reported in up to 40% of affected children. About 25% of children with rare multiple erythema migrans do have cerebrospinal fluid (CSF) pleocytosis, demonstrating a clinically nonovert dissemination of the pathogen into the central nervous system (CNS) [7].

Aside from this systemic dissemination into the skin, early dissemination mainly affects the nervous system – presenting as meningitis (CSF pleocytosis) and cranial neuritis predominantly in children. Meningoradiculoneuritis (Bannwarth's syndrome) and plexus neuritis are reported less frequently. The involvement of the heart was documented as atrioventricular blockade, myopericarditis and cardiomyopathy, but seems to be rare in both Europe and North America [8]. Early musculoskeletal complaints are reported frequently in the United States, and are less frequent in Europe. The musculoskeletal system can be involved with mild arthralgia and myalgia, in addition to a mild oligoarthritis.

In children, early dissemination and especially neuroborreliosis usually occurs earlier than in adults. This might be due to a different site of the tick bite. In children the upper trunk and the head are selected more often by the tick than in adults, potentially making the CNS more accessible to the spirochete [9].

Late stages of Lyme disease

The late stages of disease appearing months to years after infection are somewhat comparable between children and adults. In children, however, the affection of the skin and CNS are rarely seen [10]. Episodic or chronic oligoarthritis is the most frequent manifestation [11]. Neurological manifestations, more frequent in adulthood (polyneuropathy, encephalomyelitis, cranial neuropathy), are hardly recognised in children [12]. Rarely, uveitis and keratitis have been reported as late manifestations [13]. Among untreated patients in the USA, around 60% begin to have intermittent attacks of joint swelling and pain. The knees and other large joints are especially affected [1,14]. Synovial inflammation/arthritis usually is nonerosive, but can be erosive with cartilage and joint destruction – especially with chronic, persistent antibiotic-refractory arthritis. Left untreated, arthritis does show a prolonged course with a gradual, spontaneous resolution after several (up to 6) years [11]. Late skin manifestations have long been described as Acrodermatitis chronica atrophicans. Of interest, this condition has only been reported occasionally in adolescents.

Strategies proven to be effective in the treatment of Lyme borreliosis in one geographic location are often extrapolated to other regions in which the *Borrelia* species may differ and predominant clinical manifestations may vary. Because the natural history of untreated Lyme borreliosis is not delineated for all regions, it is difficult to assess whether these treatment regimens are equally efficacious across geographic regions without additional controlled studies. In addition, other tick-transmitted infections, such as babesiosis, human granulocytic ehrlichiosis and southern tick-associated rash illness, may complicate the diagnosis and treatment response, especially in the case of coinfections [15,16].

Some patients treated with antibiotics for Lyme arthritis do not experience a resolution of their arthritis, even after more than one course of treatment. The pathogenesis of this condition is not elucidated. Several hypotheses exist. Antibiotic-treatment-refractory Lyme arthritis might be rooted in a persistent infection of the pathogen suggested by the presence of borrelial DNA [17], retained spirochetal antigens with no living bacteria present [18], a pathogen-induced autoimmunity resulting from a T-cell-receptor epitope mimicry [19-21] or, finally, a nonspecific bystander immune activation. In individual patients, a predefined rheumatological autoimmunity might be unmasked by borrelial infection. In this regard, a predominance of HLA alleles DR4 and DRB1 has been associated both with chronic Lyme arthritis and adult rheumatoid arthritis in the USA [1]. In Europe, however, such an HLA association has not been elicited in affected adults and children [22,23].

The concept of molecular mimicry was suggested several years ago by identification of leukocyte function associated antigen 1 alpha as a candidate auto-antigen, which might cross-react with an outer surface protein A peptide epitope in treatment-refractory Lyme arthritis patients who express HLA-DRB1*0401 [19,21]. This concept would suggest a reactive type of arthritis being present in Lyme disease. Of particular interest is the capability of the pathogen to interact with the human immune system. At first, the innate immune system is capable of detecting the infection [24]. Sequentially the adaptive immune system is attacking the pathogen by *B. burgdorferi*-specific antibodies targeting various outer surface and structural proteins. *B. burgdorferi* is capable, however, of eliciting a variety of survival strategies inside the human host in order to circumvent the innate and the adaptive immune system. These strategies include complement resistance, antigen variation, lateral gene transfer and lipoprotein polymorphism [25]. In addition, the pathogen itself may be able to persist inside human phagocytic or tissue resident cells *in vitro* [25,26]. In the human organism, however, such a long-term persistence seems to be, if present at all, a very rare event, even though it has been suggested by some occasional case reports [27,28]. It is of interest, however, in patients with chronic treatment-refractory arthritis that *B. burgdorferi* DNA has been detected in synovial tissue, but not in synovial fluid samples even after repetitive antibiotic treatments [17]. Whether this reflects the actual presence of a viable pathogen is unclear at the moment, but is controversially debated [29].

Morphological changes of *B. burgdorferi* into the shape of cystic structures have been described in experimental environmental conditions. Again, whether this is of relevance

Table 1

Antibiotic therapy for early *Borrelia burgdorferi* infection

Early manifestations (days to a few weeks after the tick bite)		
General symptoms	Influenza-like disease	• Amoxicillin 50 mg/kg/day in three divided doses (maximum dose 1,500 mg/day) • Doxycycline 4 mg/kg/day in two divided doses (maximum 200 mg/day; after 8 years of age) for 14 days
Skin	Erythema migrans	• Amoxicillin 50 mg/kg/day in three divided doses (maximum dose 1,500 mg/day) • Cefuroxime axetil 20 to 30 mg/kg/day in two divided doses (maximum dose 1,000 mg/day) • Doxycycline 4 mg/kg/day in two divided doses (maximum 200 mg/day; after 8 years of age) for 14 days or
	Lymphocytoma	for 28 days
Neurologic disease	Lymphocytic meningitis	• Intravenous ceftriaxone 50 mg/kg/day in one dose (maximum dose 2,000 mg/day)
	Cranial neuritis, in particular facial nerve	• Intravenous cefotaxime 200 mg/kg/day in three divided doses (maximum dose 6,000 mg/day)
Cardiac disease	Myopericarditis	• Intravenous penicillin G 0.5 million U/kg/day in four to six divided doses (maximum 20 million U/day) for 14 days • Doxycycline 4 mg/kg/day in two divided doses (maximum 200 mg/day; after 8 years of age) for 14 to 28 days
Eye	Conjunctivitis (in case of influenza-like disease)	• Amoxicillin 50 mg/kg/day in three divided doses (maximum dose 1,500 mg/day)
Joint, muscle	Arthralgia	• Doxycycline 4 mg/kg/day in two divided doses (maximum 200 mg/day; after 8 years of age) for 14 days

in vivo has not been elucidated [30]. In a recent detailed structural analysis of brain tissue samples spirochetal or cystic structures have been reported in patients affected by neuroborreliosis. Control tissue of chronic brain inflammation other than borreliosis was not provided, however, limiting the evaluation of these findings [31].

There certainly is a consensus that an antibiotic treatment is of relevance in every different stage of Lyme borreliosis. What is the basis for this consensus and are there needs for a treatment beyond that?

Current treatment of Lyme disease

Prevention of Lyme borreliosis

Prevention of Lyme borreliosis after a tick bite has been reported using a single dose of doxycycline as chemoprophylaxis in America [32]. In Europe, however, a comparable prophylactic treatment has not been evaluated with regard to *I. ricinus* tick bites. The best prophylactic strategy is to avoid a tick bite. A rapid removal of a tick within 6 hours (*I. ricinus*) to 24 hours (*I. scapularis*) has been suggested [33]. The use of protective clothing and of tick repellents is advised, but this is beyond the scope of the present review.

Treatment of early manifestations

Early descriptions from America suggested that an erythema migrans can resolve spontaneously within 6 weeks, but an antibiotic treatment can shorten its duration to a few days [34]. Since then treatment studies have no longer included a placebo arm. Antibiotic treatment using doxycycline, amoxicillin, penicillin, cefuroxime axetil, ceftriaxone and recently azithromycin was focused on the outcome. In particular, an equal effectiveness in avoiding late manifestations has been shown by treatment of erythema migrans with doxycycline, amoxicillin and cefuroxime axetil for 14 days (Table 1) [35]. Oral antibiotics seem to be a sufficient treatment for solitary erythema migrans without signs of systemic disease. Extending the treatment with doxycycline from 10 to 20 days or adding an additional dose of ceftriaxone at the beginning did not improve the therapeutic efficacy in patients with erythema migrans [36]. A subsequent late stage of Lyme disease can therefore be prevented effectively by treating erythema migrans with antibiotics [37]. Since doxycycline can only be used in childhood starting at the age of 8 years and because of frequent allergies involving penicillin derivatives, azithromycin has been evaluated for the treatment of early Lyme disease. Owing to the longer half-life, treatment

duration has been limited to 5 days. Even though Massarotti and colleagues found azithromycin to be equally effective for the treatment of early Lyme disease [38], Luft and colleagues considered azithromycin to be inferior when compared with amoxicillin [39].

Overall, antibiotic treatment studies in Europe did reveal results comparable with the US examinations. Erythema migrans takes somewhat longer to resolve, however, which has been associated with the presence of three different *Borrelia* species in Europe [6,40].

About 25 to 70% of patients with erythema migrans develop nonspecific symptoms including fatigue, headache, arthralgia and myalgia, fever and lymphadenopathy, suggesting a systemic dissemination of the pathogen. In America this early dissemination is reflected in part by the presence of multiple annular skin lesions, a rare phenomenon in Central Europe. In patients with acute disseminated Lyme disease (excluding patients with meningitis, but with an erythema migrans present, in addition to signs of disease dissemination), oral doxycycline for 21 days was equally as effective in preventing late manifestations of disease as intravenous ceftriaxone for 14 days [41]. Wormser suggested that erythema migrans with uncomplicated facial nerve palsy can be treated with a 14-day course of antibiotic treatment using oral doxycycline, amoxicillin or cefuroxime in adulthood [35]. If a significant heart involvement or meningitis is present with erythema migrans, however, an intravenous antibiotic treatment regimen using ceftriaxone or cefotaxime was recommended for 14 days [35].

In paediatric patients the response to first-line treatment has been comparable with that of adults. Oral amoxicillin has been shown to be as effective as cefuroxime axetil [42]. In addition, phenoxymethylpenicillin has been shown to be effective in solitary erythema migrans [43]. The use of doxycycline after the age of 8 years has been considered reasonable in early stages of Lyme disease also in children.

Most patients treated for early cutaneous Lyme borreliosis have an excellent prognosis, although some patients treated for erythema migrans continue to have a variety of complaints after antibiotic therapy in recent series. Coinfection with infectious agents other than *B. burgdorferi* has been considered in this regard [44]. Coinfection in general, however, seems to be a rare event even in populations at high risk – it cannot be regarded as a general phenomenon [45,46]. There are no data that chronic Lyme borreliosis is associated with coinfections.

Early *B. burgdorferi* dissemination

In the second phase of infection about 15% of patients develop an acute neuroborreliosis a few weeks to months after the tick bite. Typical symptoms are cranial neuritis including Bell's palsy, meningitis and radiculitis. They are caused by meningeal inflammation, which can be accompanied by a significant headache or pain radiating into the extremities. The clinical picture of the second stage seems comparable throughout the world. In children, however, lymphocytic pleocytosis and facial nerve palsy seem to be much more common than radiculitis [47]. There are sufficient treatment reports to conclude that infection of the nervous system in both adults and children can be treated with penicillin, ceftriaxone and cefotaxime intravenously as well as doxycycline orally (Table 2). Although parenteral treatment regimens for neuroborreliosis are generally preferred, several European studies support the use of oral doxycycline with a noncomplicated CNS involvement [48].

In very rare cases, encephalomyelitis – and especially transverse myelitis – has been reported in childhood [12]. An intravenous antibiotic treatment for 14 days was effective in treating these children. Since CNS involvement in children can occur quite early (within a few days) after a tick bite, a previously *Borrelia*-nonexposed host might not be able to mount a detectable antibody response against the pathogen in such a short time [49]. Pleocytosis or facial palsy due to *Borrelia* might therefore not be distinguishable from other infectious causes like *Mycoplasma* or herpes virus infections, because serology can be unremarkable [49]. At this time, the physician might consider an additional macrolide antibiotic or antiviral treatment, especially if there are no signs of improvement during antimicrobial treatment with β-lactams [50].

In addition, corticosteroids have been recommended in Bell's palsy [50]. The authors have not found reports that corticosteroid treatment proved harmful in patients with Bell's palsy who were diagnosed with Lyme disease subsequently. Nevertheless, the usage of corticosteroids in patients with facial paralysis and highly suspected Lyme aetiology cannot be recommended and has to be considered with caution. The long-term outcome of noncomplicated neuroborreliosis (facial paralysis or pleocytosis) seems to be quite good, with minor residual facial palsies in up to 20% of patients. Cerebrovascular neuroborreliosis with signs of vasculitis and cerebral ischemia has rarely been reported in children [51].

Late stages of Lyme disease

Arthritis

In the early days of therapeutic approaches in Lyme arthritis, only very few studies have been performed in which a fraction of patients was left untreated or was treated with placebo. These patients seemed to have a prolonged course of arthritis when compared with the antibiotic-treated (penicillin or ceftriaxone) patients [11]. Nontreated patients with Lyme arthritis have been reported to suffer from ongoing chronic or episodic arthritis, or progress to other late manifestations including keratitis and chronic encephalopathy [52].

Some indirect evidence has been gathered that antibiotic treatment is indeed targeting a persistent infection: patients

Table 2

Therapy for late stages of *Borrelia burgdorferi* infection or inflammation

Late stages of Lyme disease (months to years after the tick bite)		
Skin	Acrodermatitis chronica atrophicans	• Intravenous cefotaxime 50 mg/kg/day in one dose (maximum dose 2,000 mg/day)
Neurologic disease	Meningoradiculoneuritis	• Intravenous cefotaxime 200 mg/kg/day in three divided doses (maximum dose 6,000 mg/day)
	Encephalomyelitis	• Intravenous penicillin G 0.5 million U/kg/day in four to six divided doses (maximum 20 million U/day)
Heart	Cardiomyopathy	for 14 days
Eye	Uveitis, keratitis	• Doxycycline 4 mg/kg/day in two divided doses (maximum 200 mg/day; after 8 years of age)
Joint, muscle	Episodic or chronic oligoarthritis	for 28 days For arthritis, add a nonsteroidal anti-inflammatory drug

with antibiotic-responsive arthritis did show a decline in antibody titres to *B. burgdorferi*, whereas antibody titres remained high in patients who were left untreated. Patients who presented with persistent arthritis despite antibiotic treatment also showed a decline in antibody titres. This suggested that synovial inflammation persisted in these patients after the infection was cleared by the use of antibiotics [53]. The studies conducted, however, have not tried to evaluate a principal anti-inflammatory effect of antibiotics. Steere and Angelis reported on their initial, untreated Lyme arthritis cohort. Arthritis eventually resolved after a disease duration of about 6 years or longer in children, adolescents and adults [11]. In the author's own experience, however, there are a few patients who eventually continue to have chronic arthritis despite several antibiotic treatments according to European guidelines [54]. In these patients, local inflammation stays active and significant antirheumatic treatment strategies are necessary. Which particular patient does not benefit from antibiotic treatment and who is prone to proceed to long-term Lyme arthritis is not clear. As already mentioned, immunological features, genetic factors and pathogen-related factors might all contribute to the evolution into a rheumatoid-like disease. Even though a significant portion of treatment-refractory patients with Lyme arthritis has been noted in several studies, the general consensus is that antibiotic treatment remains the cornerstone of therapy [11,40].

Steere and Angelis recently formulated a treatment algorithm for the diagnosis and treatment of Lyme arthritis. As an initial treatment they suggest using oral doxycycline or oral amoxicillin for 30 days. They proposed a repetition of the oral antibiotic regimen for another 30 days if a mild arthritis persists after the first-line treatment was completed 30 days ago. An intravenous antibiotic treatment using ceftriaxone, cefotaxime or penicillin for 30 days was recommended if a moderate to severe arthritis persists. The basis for this suggestion, especially the reason for the prolongation of treatment up to 30 days, was not made clear. This suggestion has to be considered an expert opinion [11]. In comparison, other authors have reported that penicillin G is not as effective as ceftriaxone for the treatment of late Lyme manifestations [55].

Significant side effects using an intravenous treatment strategy for longer than 14 days have to be considered. The authors of the present review suggested a repetition of antibiotic therapy in antibiotic-refractory Lyme arthritis for the duration of 14 days with a preference of using intravenous cefotaxime in an inpatient setting (three divided doses) [54]. Cefotaxime seems to have lesser side effects than ceftriaxone with regard to complications of bile secretion.

In an outpatient setting, intravenous ceftriaxone for the duration of 14 days would be the first choice (one daily dose). Reviewing the work of Steere and Angelis, a significantly greater number of doxycycline-treated patients (45 out of 71) did respond to therapy when compared with five out of 46 patients who responded after intravenous ceftriaxone. This remarkable failure rate using ceftriaxone as a first-line agent was left unexplained [11]. For children older than 8 years of age, arthritis can be treated using doxycycline in a dose of 4 mg/kg/day [54] (Fig. 1). From a rheumatological point of view, it is striking that in almost all of the Lyme arthritis studies reported, no concomitant anti-inflammatory therapy has been evaluated. Our experience is that the parallel usage of nonsteroidal anti-inflammatory drugs right from the beginning does reduce symptoms of inflammation and contributes to a faster resolution of arthritis, even though no prospective long-term data are available.

In children and adolescents, treatment guidelines in Europe do include the usage of nonsteroidal anti-inflammatory drugs in parallel to antibiotics. There was a consensus that the second round of antibiotic treatment should not exceed a time period of 14 days with intravenous antibiotics or 4 weeks

with oral doxycycline [54]. If arthritis persists after two complete courses of antibiotic treatment and sufficient non-steroidal anti-inflammatory drug treatment, intra-articular steroids and the use of disease-modifying antirheumatic drugs should be considered [54]. Arthroscopic synovectomy has been reported occasionally [11]. A further prolongation of the antibiotic treatment was suggested in case the synovial fluid or tissue analysis does reveal the presence of *B. burgdorferi* DNA. This suggestion can be considered of expert level and is not based on controlled studies [11]. It is not clear whether such a positive PCR represents the presence of a viable pathogen or simply nondegraded DNA, and whether this finding is of clinical relevance.

A prospective treatment study was reported from a European childhood cohort in 1995 [23]. The response rate after one or two courses of different antibiotics resulted in a disappearance of arthritis in 77% of the patients [56]. Szer and colleagues reported on the long-term follow-up of patients initially followed by Steere and colleagues who were not treated with antibiotics. Only a few patients were reported to suffer from ongoing chronic or episodic arthritis, or progress to other late manifestations including keratitis and chronic encephalopathy [52]. The scarcity of the studies on long-term outcome does reflect an urgent need to perform follow-up studies even on a retrospective basis. In addition, a long-term prospective controlled trial is warranted in order to further elucidate the beneficial role of antibiotics in children. It seems reasonable to consider conventional anti-inflammatory drug treatment for arthritis already from the start together with antibiotics.

Late neurological disease

Peripheral polyneuropathy (paresthesia), meningoradiculoneuritis (radicular pain), encephalopathy (memory loss, mood changes, sleep disturbance) or encephalomyelitis do represent late neurological manifestations in adulthood [57]. Treatment efforts using antibiotics (Table 3) usually are effective [57]. In childhood, neurological disease is predominantly an early manifestation (CSF pleocytosis, facial palsy) but also can present as radiculitis in older children [58]. Late manifestations have to be considered very rare.

Late skin disease

Late skin manifestations are usually caused by *B. garinii* and *B. afzelii*, and are thus seen predominantly in Europe and not in the USA. Acrodermatitis chronica atrophicans is caused by *B. afzelii* and is characterised as a blue/red-coloured atrophic skin lesion predominantly at the extremities [59]. Antibiotic therapy for at least 4 weeks has been recommended (Table 3) [60].

Post-Lyme disease syndrome

Despite the resolution of Lyme borreliosis manifestations after antibiotic treatment in the majority of patients, a minority of patients present fatigue, musculoskeletal pain, concentration or short-term memory problems. These generally mild and self-limiting symptoms have been termed post-Lyme disease symptoms. If the symptoms last longer than 6 months they have been called post-Lyme disease syndrome.

In contrast to the late manifestations of antibiotic-refractory arthritis and post-Lyme disease symptoms/syndrome, there is a group of patients with chronic pain, neurocognitive symptoms, fatigue, and so forth. In some of these patients the diagnosis of chronic Lyme disease has been made without clinical or serological evidence of a current or previous Lyme disease. There have been attempts to define the pathogenesis of this particular complex of symptoms. Not yet standardised diagnostic tests to detect *B. burgdorferi* immunoreactivity have often been implemented. Recent studies, which have tried to define these patients more clearly, in general point towards other causative differential diagnoses including fibromyalgia or other autoimmune musculoskeletal diseases [61-63]. Intravenous or oral antibiotics for a prolonged period of time or repetitively did not improve symptoms in these particular patients [61]. Nevertheless there is still a major controversy in the literature and in the press requesting long-term antibiotic treatment for these patients [29,64].

To make things difficult, a few arthritis patients have been described with evidence that *B. burgdorferi* DNA persisted in the joint without anti-*B. burgdorferi* antibodies present in their peripheral blood [65]. The cause of seronegativity is unknown. One possible cause might be the formation of immune complexes involving antigen-specific antibodies. Since routine serodiagnostic tests rely on free antibodies, antibodies tied up in complexes would not be detectable [66]. In the majority of patients suffering from late Lyme disease, however, a robust antibody response is present. There might be only very few individuals affected by Lyme arthritis or post-Lyme disease syndrome who do not have a detectable serological response to the pathogen. Seronegative patients without clinical signs of classical Lyme disease but with chronic fatigue, arthralgia and myalgia did not respond to antibiotics even when multiple courses of treatments were given. This study was also interpreted in a way that serological tests can reliably rule out Lyme borreliosis in patients with these chronic symptoms, thus preventing unnecessary treatment with antibiotics [67]. For the majority of chronic Lyme disease patients, other differential diagnoses should be considered. This could avoid long-term, and therefore potentially side-effect-prone, antibiotic treatment. As can be expected, there is a lot of controversy on the subject of chronic Lyme disease [29,62,68].

Strategies to generate a vaccine against *Borrelia*

Several significant obstacles have to be overcome before a vaccine can be considered effective in the context of the complex tick–host–pathogen interaction in Lyme borreliosis.

Table 3

Therapy for persistent Lyme arthritis refractory to the first antibiotic treatment

Persistent Lyme arthritis		
Antibiotic-refractory persistent arthritis	Significant inflammation (effusion, limited range of motion, oligoarthritis)	Repeat • Intravenous cefotaxime 50 mg/kg/day in one dose (maximum dose 2,000 mg/day) • Intravenous cefotaxime 200 mg/kg/day in three divided doses (maximum dose 6,000 mg/day) • Intravenous penicillin G 0.5 million U/kg/day in four to six divided doses (maximum 20 million U/day) for 14 days up to 28 days
	Limited inflammation (for example, monoarthritis)	• Doxycycline 4 mg/kg/day in two divided doses (maximum 200 mg/day; after 8 years of age) for 28 days Additional anti-inflammatory therapy: nonsteroidal anti-inflammatory drugs
No remission reached	In synovial fluid or synovia:	Prolong antibiotic oral treatment for another month
	B. burgdorferi DNA present	Consider • Intra-articular steroid injection • Disease-modifying antirheumatic drug therapy • Arthroscopic synovectomy
	B. burgdorferi DNA not present	Consider • Intra-articular steroid injection • Disease-modifying antirheumatic drug therapy • Arthroscopic synovectomy

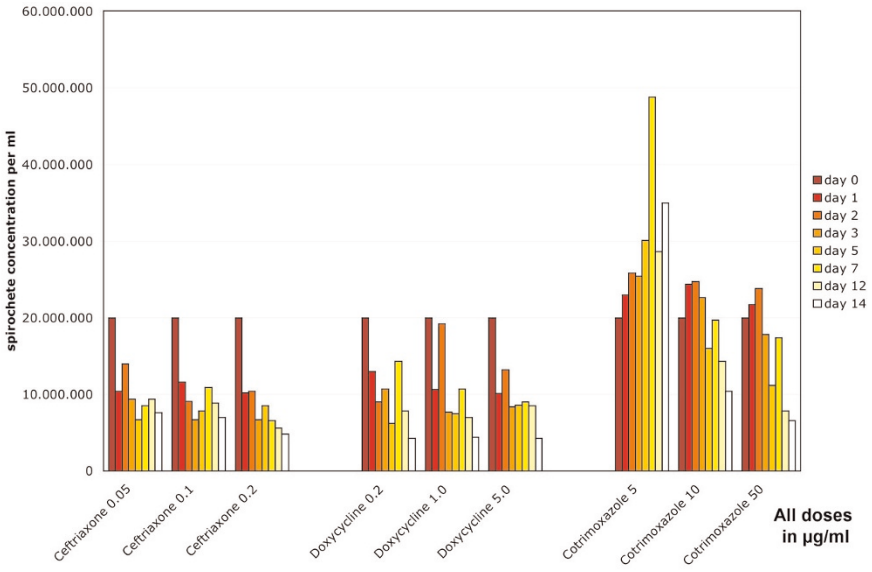
B. burgdorferi is able to mount molecular survival strategies in order to circumvent the host's immune defence mechanisms [25]. In addition, persistence in bradytrophic tissues might render the pathogen inaccessible for the immune system [27].

B. burgdorferi not only manipulates human resident tissue cells and members of the immune system, but also interacts with the gene expression profile of the tick vector. The latter strategy enables the pathogen to survive within the tick and during the transmission process. Some of these tick gene products might be potentially valuable in developing a vector-antigen-based vaccine [69]. These vector-based vaccine targets, however, are just at the beginning of being evaluated.

In the early 1990s, the major outer-surface protein (Osp) A and OspB were already considered interesting targets for a pathogen-based vaccine [70]. Since only one *B. burgdorferi* genotype is present in the United States, two recombinant OspA vaccine preparations were eventually tested in adults as well as in children – the vaccines were considered safe and their immunogenicity to be sufficient to mount an anti-OspA immune response [71]. It was of particular immunological interest that the recombinant OspA vaccine was able to block transmission of the spirochete from the vector to the host by virtually sterilising the infected vector. During the blood feast, OspA-specific antibodies were transferred from the immunised host to the vector. These transferred antibodies did interfere with the complex lifecycle of the spirochetes, which express OspA especially inside the tick. Success of the vaccine in murine animal models [72] was the basis for these human studies [73]. Subsequent analyses of the cost-effectiveness revealed that individuals who live in areas where Lyme disease is endemic and who are frequently exposed to ticks are the best candidates to be vaccinated [74]. Despite clinical effectiveness and no significant side effects reported, Lyme disease vaccines have been taken off the market or are no longer propagated. Fears that an OspA-based vaccine could itself induce an autoimmune disease by induction of a cross-reactive immune response might have contributed to low sales of the vaccine and its final withdrawal from the market.

Owing to the presence of several *Borrelia* genotypes in Europe, a monovalent vaccine is not considered effective throughout Europe. Different vaccine targets therefore have to be considered. In addition, due to molecular strategies of the Lyme disease spirochete *B. burgdorferi*, including antigenic variation and immune escape, complement resistance as well as lateral gene transfer, one particular preventive strategy seems insufficient to induce long-term protection [25].

Figure 1



In vitro antimicrobial susceptibility of *Borrelia burgdorferi* sensu strictu. Reduction of viable spirochetes in the presence of different concentrations of antibiotics (ceftriaxone, doxycycline). Cotrimoxazole, which is considered ineffective, is used as a control. Only in high doses does cotrimoxazole show a reduction in the amount of spirochaetes after a few days. Tests were performed on microtitre plates by broth dilution; spirochete count determined by dark-field microscopy.

Conclusion

Even though Lyme borreliosis is considered an infection, and despite high antibiotic sensitivity of the pathogen, a limited number of patients treated for late-stage disease remain symptomatic despite antibiotics. The reason for persistent symptoms is unclear. Several pathogen-related and host-related factors have been suggested. There is considerable lack of knowledge on the natural course of disease in different environments and with regard to different genotypes or even strains of *B. burgdorferi* sensu lato. Coinfections may complicate the picture even further.

Current knowledge of the effectiveness of antibiotic treatment strategies is based on a very limited number of trials, which have not been evaluated sufficiently long term and which often lack a placebo-controlled arm. In addition, the number of patients included has to be considered limited, as no large double-blind, controlled, long-term prospective trials have been performed. Unsurprising, therefore, is the considerable uncertainty of which antibiotic regimen should be chosen and which duration of therapy should be performed. For the time being, guidelines for antibiotic treatment have been suggested that are successful in about 80% of patients affected by late stages of *B. burgdorferi* infections.

Overall, the outcome of early and late manifestations seems to be good; nevertheless, there is an urgent need to develop strategies for those patients who do not respond completely to the current treatment concepts.

Competing interests

The authors declare that they have no competing interests.

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