Infectiologic differential diagnosis of chronic Lyme disease and so-called coinfections

by

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Summary In cases of Lyme disease (LD), other infections can be concurrently present; their pathological synergism exacerbates the disease state or induces the same disease manifestations. Such concomitant infections are termed coinfections. The coinfections can also be transmitted by ticks as LD is, i.e. a tick bite can result in multiple infections. A fraction of the coinfections is transmitted independently of ticks or in addition to tick transmission there are other modes of transmission. The clinically relevant coinfections are caused by Bartonella species, Yersinia enterocolitica, Chlamydophila pneumoniae, Chlamydia trachomatis, and Mycoplasma pneumoniae. In contrast to the USA, human granulocytic anaplasmosis (HGA, previously called human granulocytic ehrlichiosis (HGE)) and babesiosis are not of major importance in Europe. The "coinfections" can, of course, also occur without connection to the LD and in some cases independently result in pronounced disease symptoms, which exhibit substantial instances of overlap with LD's clinical picture. This applies particularly to infections caused by Bartonella henselae, Yersinia enterocolitica, and Mycoplasma pneumoniae. Chlamydia trachomatis primarily results in arthritides; Chlamydophila pneumoniae additionally causes disease manifestations of the nervous system and of the heart. This makes differential diagnosis very difficult; in some cases, impossible. Even more problematical is the diagnosis situation when coinfections occur in association with LD, i.e. when double and multiple infections exist. — The pathological importance of the coinfections was first recognized in the 1990s, i.e. approximately ten years after the discovery of LD. No studies exist on the treatment of coinfections; the therapy recommendations are based on individual expert opinions. In antibiotic treatment, the use of 3rd generation cephalosporins should only be considered in cases of Lyme disease. The same applies to carbapenem, which is also occasionally used in infections caused by Yersinia enterocolitica subsequent to testing. For the remaining infections tetracyclines and macrolides are predominantly used; quinolones are an alternative, particularly gemifloxacin. For Bartonella henselae, Chlamydia trachomatis, and Chlamydophila pneumoniae the combination with rifampicin is recommended. Erythromycin is the pharmaceutical agent of choice for Campylobacter. The symptomatology and antibiotic treatment of the infectious diseases are presented in tabular overviews at the end of the text.

In cases of Lyme disease (LD), other infections, whose pathological synergism exacerbate the disease state or induce the same disease manifestations, can exist concurrently. Such concomitant infections are termed coinfections. The coinfections can also be transmitted by ticks as LD is, i.e. a tick bite can result in multiple infections. A fraction of the coinfections is transmitted independently of ticks, or in addition to tick transmission there are other modes of transmission.

The coinfections that are transmitted by ticks are given in Table 1; the coinfections that are independent of ticks are compiled in Table 2.

The coinfections favor the expression of disease states by means of immune system modulation and are considered to be a major reason for therapy resistances [176 - 192].

The importance of the coinfections for the pathological process—i.e. their pathogenicity compared to Lyme disease—has not been clarified. Thus, in cases of double or multiple infections, a decision cannot be made as to which infection dominates in the pathological process.

In the symptomatology there are substantial overlaps between Lyme disease and the coinfections so that an unequivocal assignment of the disease manifestations to the existing infections is impossible. Many symptoms can thus be due to both a Lyme disease and the so-called coinfections.

The problematic nature of Lyme disease and coinfections always concerns the chronic course. The coinfections are thus only of importance for chronic Lyme disease (late stage, stage III). On the other hand, the synergic-pathological mechanism requires that the coinfections also are present in a chronic persistent form.

Anamnistically, one has to consider whether coinfections occurred in their acute form in the early phase because this contributes to the recognition of coinfections in the chronic phase.

In terms of laboratory diagnostic tests, only methods for indirect pathogen detection (serology, LTT) are also available for the coinfections in most cases, as is the case for Lyme disease. The prior infection can be confirmed with serological investigations. However, a positive serological finding is not proof that the infection caused the current illness. Basically, it is neither possible to prove the presence of an infectious disease nor to exclude it by means of a serological finding. Only if pathological laboratory findings occur or a deterioration of the finding can be detected in correlation with the disease are conclusions as to the disease development and situation justified to a certain degree in cases of previous seronegitivity or negative LTT in temporal parallelism to disease development.

The significant coinfections of Lyme disease are caused by Bartonella species (primarily by B. henselae), Chlamydia trachomatis, Chlamydophila pneumoniae, Yersinia enterocolitica, and Mycoplasma pneumoniae. Accordingly, these infectious diseases are highlighted in Tables 1 and 2 by the typeface.

Table 1
LD coinfections (tick-borne)

Disease*	Pathogen
HGA (Synonym HE)	Anaplasma phagocytophilum
Bartonellosis	Bartonella henselae (B. quintana B. bacilliformis)
Rickettsiosis	Rickettsia helvetica
Mediterranian spotted fever	Rickettsia conorii
Tularemia	Francisella tularensis (Other transmission modes: Mosquitos, Gadflies, fleas, lice, mites, oral, inhalation)
Q fever	Coxiella burnetii (Transmission also oral or by inhalation)
Babesiosis	Babesia bovis (Switzerland) Babesia microti (Poland)

Table 2
LD coinfections (not tick-borne)

Disease*	Pathogen
Mycoplasma infections	Mycoplasma pneumoniae
Chlamydophila pneumoniae infection	Chlamydophila pneumoniae
Chlamydia trachomatis infection	Chlamydia *trachomatis*
Yersiniosis	Yersinia enterocolitica (Y. pseudotuberculosis (USA))
Parvovirus B19 infection	Human parvovirus B19

* The relevant coinfections are highlighted in bold type.

The frequency of seropositivity and positive LTT (lymphocyte transformation test) was studied on my own clientele (n = 108). The results are presented in Table 3. The investigations were conducted at the Institute for Medical Diagnostics (IMD) in Berlin. For more detailed information, please refer to the corresponding reference [339]. An LTT is not available for Bartonella. An LTT was not performed for Mycoplasma pneumoniae. The high incidence of the Chlamydia trachomatis LTT is conspicuous and unresolved.

Table 3
Seropositivity and positive LTT with regard to coinfections in %
(in patients with chronic Lyme disease)

	Seropositivity	Positive LTT
Mycoplasma pneumoniae	36	-
Chlamydophila p.	62	66
Chlamydia *trachomatis*	5	100
Yersinia enterocolitica	58	50
Bartonella henselae	78	-

According to investigations on my own clientele, CD57 NK cells are frequently diminished in chronic Lyme disease, but seldom in cases involving coinfections. However, the basic principle is that CD57 NK cells can be diminished in all chronic infectious diseases, but the phenomenon is observed relatively frequently in chronic LD.

The more important coinfections are summarized in an overview (Table 4). These more important coinfections are presented in accordance with the tabular sequence; they are then followed by the less important ones (chapter “Secondary coinfections of Lyme disease”) and finally to round out the presentation, a chapter on the so-called reactive arthritis follows.

In contrast to the USA, HGA (human granulocytic anaplasmosis, syn. human granulocytic ehrlichiosis (HGE)) and babesiosis are of little importance as coinfections in Europe.

Table 4
Important LB coinfections

Disease*	Pathogen	Mode of transmission
Bartonellosis	B. henselae (B. quintana B. bacilliformis)	Manifold, see Tab. 5
Chlamydophila Pneumoniae infection	Chlamydophila p.	Droplet infection (person to person)
Chlamydia *trachomatis* infection	Chlamydia tr.	Sexual
Yersiniosis	Yersinia enterocolitica (Y. pseudotuberculosis (USA))	Fecal-oral
Mycoplasma pneumoniae Infection	Mycoplasma pneumoniae	Droplet infection (person to person)

Bartonellosis

Many interrelationships in the bartonellosis’ mode of transmission have not yet been clarified. The important infection data described in the scientific literature are summarized in Table 5.

Table 5
Bartonellosis' infection data

Pathogen:

- B. henselae
- B. bacilliformis)
- (B. quintana
[66, 67, 68]

Transmission:

- Cats (scratches, bites)
- Dogs (scratches, bites)
- Cat fleas
- Lice (B. quintana) [130]
[69]

Other modes of transmission:

- Dust mites
- Flea bites
- Flea feces (oral infection)
- Contact with cats
- Contact with dogs
(paws, saliva
- Lice [130]
- Flies
- Mother-child transmission
[101]

Reservoir:

- Cats [71-74]
- Domestic and wild animals [70]

Intracellular localization

Primary manifestations: infected skin lesion, swollen lymph nodes, multiorgan disorder (e.g. liver, spleen, nervous system, eye) [66-67], cf. Tab. 6.

Until 1993 only B. bacilliformis was known. The different Bartonella subspecies were first described [69] and their pathological significance, recognized in 1993

Bartonellosis can be expected to have substantial significance as a Lyme disease coinfection. With regard to the health policy aspect, Lyme disease is more important because of its frequency. However, in this context it should be noted that bartonellosis has not been nearly as intensively investigated as Lyme disease. Additionally, it is obvious from my own observations that the serology for Bartonella is frequently positive in patients with chronic Lyme disease.

With the increasing development of laboratory tests which is to be expected, the currently underestimated prevalence of bartonellosis will be more correctly registered in the future, and the importance of this disease will also be determined on the basis of its frequency.

Bartonellosis (caused by B. henselae und B. bacilliformis) can be associated with an extraordinary variety of symptoms. For further information on this see Table 8.

The bacterial-inflammatory skin infection (scratch or bite location) is in no way obligatory, i.e. bartonellosis can also occur without the typical cat scratch disease, which is characterized by the infected skin lesion and lymph node swelling.

Bartonellosis' disease morphology can be better recognized when the most important of its many symptoms (Table 8), i.e. its main manifestations, are considered (cf. Table 6).

Table 6
Main disease manifestations of bartonellosis

(Cat scratch wound)
(Contact with cat fleas)
(Tick bite)
(Louse infestation)
(Other infection data see Tab. 5)

— Infected scratch or bite wound (cat, dog)
— Lymph node swelling (regional or generalized [75])
— Persistent fever of unknown origin
— Abdominal pains, loss of weight [69]
— Various eye disorders [76]
— Neuroretinitis [77, 78, 79]
— Neurological manifestations [80 - 82]
- Encephalopathy (very frequent)
- Transverse myelitis
- Neuroradiculitis
- Cerebellar ataxia
- Cerebral seizures [81]
- Cerebral infarction due to vasculitis [81]
- Liquor: mild mononuclear pleocytosis [80]
- Pathological EEG

— Musculoskeletal complaints [83]
- Arthritis
- Arthralgias
- Myalgias
- Tendinitis
(chronic course of arthropathies [83, 84])

— Fatigue [85]
- ESR and CRP elevated

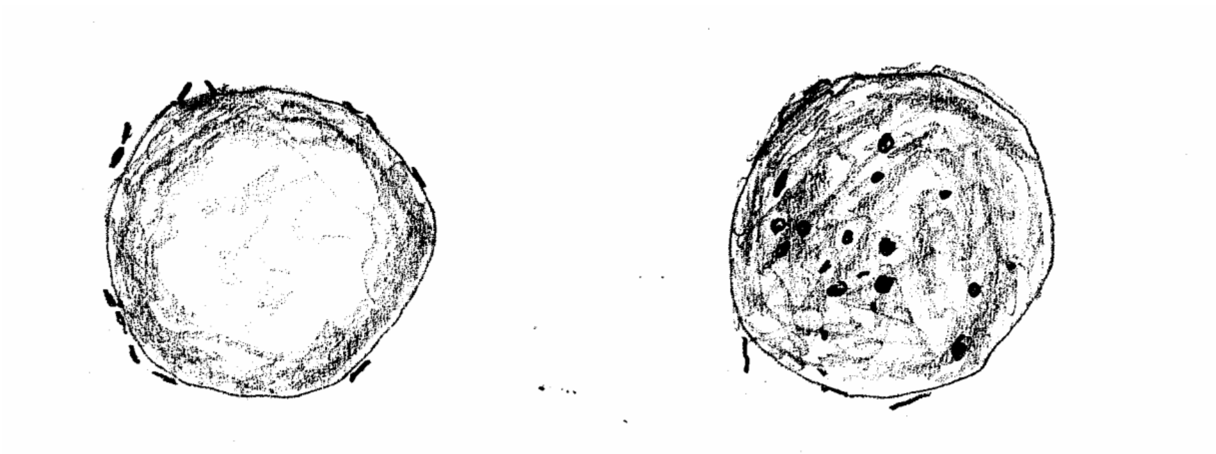
There are numerous overlaps with Lyme disease in the disease manifestation of bartonellosis. This fact is also mentioned in the relevant current literature [86].

The laboratory diagnostics for bartonellosis is given in Table 7.

Table 7
Laboratory diagnostics for bartonellosis

- Blood smear
- Serology
- Pathogen detection using culture methods
- Pathogen detection using PCR
- Histopathological investigations

In cases of infection with Bartonella, the blood smear initially shows pathogens on the outer membrane; in the further course the pathogens are increasingly localized intracellularly. In the process, the light colored center of the erythrocytes is lost (Fig. 1).



A. B.

Fig. 1. Erythrocytes infected with Bartonella henselae (Bh). A. Early stage, Bh on the outside of the erythrocytes; b. With increasing duration of infection, Bh primarily intracellular; erythrocytes loose their light-colored center.

There is no information on the value of serology in the literature. In particular, the question as to whether seronegativity rules out the disease has not been clarified. On the other hand, as is the case for many other infectious diseases, a positive serological finding merely proves that an infection took place, but does not indicate that the disease currently exists.

Detecting Bartonella in culture is extremely problematical, and the sensitivity is very low so that this method of investigation is not part of routine diagnostics.

Detection of pathogens using PCR in biopsies appears to be very promising [87, 232], but the investigation with PCR must follow the biopsy nearly immediately [88].

The chronic course of bartonellosis has been described in numerous studies, in part, on large groups [90 - 94]. The long duration of the disease, which frequently covers many years, and the high similarity of the disease manifestations makes it extremely difficult to distinguish from chronic Lyme disease. Thus, bartonellosis is of great importance in the infectiologic differential diagnosis of Lyme disease.

In this context, attention should be paid to the fact that B. henselae has been found in ticks and that the transmission of B. henselae by ticks has been documented by means of pathogen detection in the liquor [95]. Additionally, the prevalence of B. henselae in ticks is apparently high; scientific studies determined a prevalence of 40% [96].

According to my own surveys, 78% of the patients with chronic Lyme disease proved to be seropositive for Bartonella henselae.

A particular characteristic of Bartonella is the induction of vascularized tumors or granulomas, which occur in the region of the skin (bacillary angiomatosa), in the liver (peliosis hepatis) or in the spleen (peliosis splenitis) [97 - 99]. In this context, these vascular tumors or granulomas exhibit a pathological sprouting of capillaries as well as enlarged and hyperproliferative vascular endothelial cells [100]. Bartonellosis is obviously accompanied by a stimulation of blood vessel formation. This corresponds to the observation that bartonellosis, in addition to angiomatosis, also results in different other skin manifestations in which an increased vessel formation is observed [101]. In addition, the determination of VEGF (vascular endothelial growth factor) in blood could be of diagnostic importance [101].

In all pathogenetic relevant bartonellae (B. quintana, B. henselae, B. bacilliformis), this effect on endothelial cells and the induction of angiogenesis has been demonstrated. In the process, the vascular proliferation was primarily traced back to three factors [102 - 108]:

- Elevated endothelial cell proliferation
- Inhibition of the apoptosis of endothelial cells
- Increased secretion of vasculoproliferative cytokines

All these studies support the idea that VEGF (vascular endothelial growth factor) plays a significant role in Bartonella-induced endothelial cell proliferation [108].

Bartonellae are localized in erythrocytes and cause deformations of the erythrocyte membrane [110 - 111].

The visualization of the bartonellae in erythrocytes is already being used diagnostically, particularly also with regard to the extent of the infection [101]. However, irrefutable literature on erythrocyte infestation in chronic bartonelloses does not exist. The diagnostic value of a new method of detecting pathogens by means of cilia in blood smears cannot be assessed yet.

The formation of intracellular blebs subsequent to penetration into the endothelial cells has also been determined for Bartonella quintana, i.e. a similar process to that in Lyme disease. Moreover, Borrelia burgdorferi also has a high affinity for endothelial cells, and the development of blebs, particularly in chronic disorders, has been described. In connection with Lyme disease, the intracellular presence of the pathogen and the formation of biologically less active eukaryotic forms (cyst forms, blebs) have been discussed as the cause of the failure of antibiotic treatment. In addition, parallels between Lyme disease and bartonellosis have been found [cf. 112 - 117].

Table 8
Symptomatology of bartonellosis

Transmission modes /Vectors:
Bite or scratch wounds (dog, cat)
(saliva, claws)
Flea bites
Flea feces (oral)
Lice
Flies
Gadflies
Dust mites
Blood transfusions
Mother-child transmission

Infected scratch or bite wounds
Lymphadenopathy
(frequently cardinal symptom)

General symptoms
Fever
Fatigue
Drowsiness
Sleep disorders
Obesity
Swelling in different parts of the body
Sleep disorders
Weariness
Headaches
Air hunger
Fainting fits

Encephalopathy
Cognitive disorders
Concentration disorders
Blockage of thought processes
Limited memory
Instances of dyslexia and dysgraphia

Mental disorder:
Depression
Irritability
Agitation / Aggression
Disturbed impulse control
Panic attacks

Nervous system
Encephalitis
Myelitis
Neuralgias
Muscular asthenia
Paresthesias
Neuroradiculitis
Seizures
Cerebral infarction
Guillain-Baré syndrome

Musculoskeletal system
Arthritis
Arthralgias
Myalgias
Tendinitis
Osteomyelitis
Myospasm

Abdomen
Hepatopathy
(Peliosis hepatis)
(Hepatomegaly)
Splenopathy
(Peliosis splenitis)
Splenomegaly
Abdominalgia
Hepatic and splenic abscesses

Heart / Thorax
Endocarditis
Pneumonia
Pleural effusion
Myocarditis

Eye
Oculoglandular disorder
Conjunctivitis
Neuroretinitis
Papillitis
Optic neuritis
Retinochoroiditis
Uveitis: anterior, intermedia and posterior [233]
Acute maculopathy
Choroiditis

Urogenital system
Bladder disorder
Renopathy
Genital disorders

Skin
Bacillary angiomatosis
Striae
Papule
Edema
(particularly of the feet)
Acne
Occurrence of venous vessels at an unusual location
Hyper- or hypopigmented skin
Pea-sized pigment spots
Burgundy-colored, thin skin
Lesions in the area of the oral mucosa
Morphea
Patchy loss of hair
Loss of eyelashes
Change in hair color in hypopigmented areas
Diffuse patchy exanthema
Signs of hypervascularity
Hematoma-like changes
Skin lesions with indentation
Pigment spots
Erythema nodosum

Other
Parotid swelling
Phlegmonous abscess in the neck region
Septic shock
Thrombocytopenic purpura
Overproduction of calcitriol

Laboratory findings
ESR und CRP elevated
Hypercalcemia

For completeness sake, two additional forms of bartonellosis are mentioned, namely Oroya fever or verruga peruana and trench fever.

Oroya fever and Verruga peruana are a Bartonella bacilliformis infection, which is transmitted by sand flies. The disease occurs in the Andes. The acute form affects tourists who are immunologically naive with respect to B. bacilliformis. Without treatment the mortality rate is 40%. To date, the factor which results in the severe disease course in this context is unknown.

Oroya fever and its recognition as an infectious disease date back to Carrion, who verified that the disease is infectious in a fatal self-test at the end of the 19th century.

Trench fever was discovered at the beginning of the 20th century. Its transmission occurs via lice [127 - 129]. In 2002 the pathogen was detected for the first time in erythrocytes; as a result the transmission by lice became plausible [130].

No adequate studies exist for the treatment of bartonellosis. There is not a single treatment method that has been approved by the FDA, CDC or IDSA [101]. This applies particularly for chronic courses [123].

The antibiotic treatment is given in Table 9. The following antibiotics are recommended: azithormycin [118, 199], rifampicin, ciprofloxacin, trimethoprim + sulfamethoxazole, gentamycin [120, 122], gentamycin i.v. [121], doxycycline + gentamycin [124, 125].

The treatment is based, in part, on expert recommendations [126]. Other references are listed in Table 9.

Table 9
Antibiotic treatment of bartonellosis

Antibiotic	Dose/ day	References
Azithromycin	500 mg	[118, 199, 323, 325, 326, 328, 329, 330, 337, 338]
Clarithromycin	1000 mg	[323, 326, 328, 329, 330, 331, 337, 338]
Telithromycin	800 mg	[323]
Rifampicin	600 mg	[120, 122, 323, 325, 326, 329, 337, 338]
Trimethoprim-Sulfamethoxazol	875 / 125 mg 2xdaily.	[120, 122, 328, 330]
Ciprofloxacin	1000 mg	[120, 122, 323, 328, 329, 330]
Doxycycline	400 mg	[124, 323, 325, 326, 330, 337, 338]
Minocyclin	200-300 mg	[329]

(Other recommendations: erythromycin, roxithromycin, penicillin G, sparfloxacin, chloramphenicol, streptomycin, gentamycin, Augmentin, ticarcillin, cefotaxime, ceftriaxone, meropenem, trimethoprim and sulfamethoxazole. The information in the various publications is very contradictory. This is particularly true for gentamycin. Beta-lactam antibiotics do not act intracellularly and are therefore not suitable for the treatment of bartonellosis (author's comment) [120, 121, 122, 125, 323, 324, 325, 326, 327, 329, 330, 331, 335, 336, 337]. There are substantial discrepancies between in vitro findings and in vivo efficacy.

Duration of treatment (no reliable data basis)	
Acute early phase	2 weeks
Chronic course	2 - 3 months

The discrepancy between the in vitro findings and the in vivo results is set out in various publications [324, 329, 331, 333, 336].

Since Bartonella henselae is primarily localized intracellularly in vivo, only antibiotics that act intracellularly are used; they are listed in Table 9.

Because instances of non-response and recidivation are not seldom in cases of chronic bartonellosis, long-term antibiotic treatment is recommended [322, 323, 324, 333, 336].

The efficacy of aminoglycosides (particularly gentamycin) is extremely controversially assessed. Publications with a positive assessment [324, 328, 330, 336, 337] are in opposition to other contributions which assess aminoglycosides as ineffective or insufficiently effective [325, 326, 329].

Chlamydophila pneumoniae

Chlamydophila pneumoniae is important in the differential diagnosis of Lyme disease because of the following disease manifestations.

- Disorders of the nervous system
- Reactive arthritis
- Myocarditis

Chlamydias have special microbiological characteristics: The size of the pathogen is very small compared to other bacterial strains; reproduction occurs only within the host cell; the pathogen is dependent on the host cell's ATP because it is not able to produce its own.

The pathogen exhibits two phenotypes:

- Elementary bodies
- Reticulate bodies

The elementary bodies can exist extracellularly and are the infectious form. Reproduction of the elementary bodies is only possible in the host cells. After penetration, the elementary bodies are phagocytized by the host cell; intracellularly the elementary body changes into the reticulate body and as such can again divide. The elementary bodies are thus infectious, and the reticulate bodies are reproductive. Some reticulate bodies change back to elementary bodies, which are released subsequent to lysis of the host cell. The thus-produced elementary bodies then infest further host cells. Consequently, the precondition for an effective antibiosis is that the antibiotic is both intracellularly and extracellularly effective. This is the case for tetracyclines and macrolides.

The infection data for Chlamydophila pneumoniae are summarized in Table 10.

Table 10
Infection data for Chlamydophila pneumoniae

Pathogen:

- Chlamydophila pneumoniae

Transmission:

- Droplet infection
- Person to person

Reservoir:

- Human beings

Primary manifestations:

- Pneumonia
- Disorders of the nervous system
- Reactive arthritis
- Myocarditis

Intracellular and extracellular localization

The primary disease manifestation of Chlamydophila pneumoniae is pneumonia. The incidence is 1% and predominantly affects people older than 65 years of age [132, 133]. The pneumonia is frequently accompanied by infections of the upper respiratory tract (pharyngitis, laryngitis, sinusitis). Slight disease expression initially, extrapulmonary manifestations (see Tab. 11) and a normal leukocyte count indicate an atypical pneumonia and thus also pneumonia caused by Chlamydophila pneumoniae.

In addition to pneumonia, Chlamydophila pneumoniae causes extrapulmonary manifestations [134] (cf. Table 11), which are significant with regard to the differential diagnosis of Lyme disease (LD) or Lyme neuroborreliosis (LNB).

Table 11
Extra pulmonary manifestations of Chlamydophila pneumoniae infections

Meningoencephalitis
Guillain-Barré syndrome
Reactive arthritis
Myocarditis

(The extra pulmonary manifestations have differential diagnostic reference to LD and LNB)

The chronic course of Chlamydophila pneumoniae infections is documented by studies [234 - 240]. A relationship to CP was also described for Alzheimer's disease [241]. This is a finding that is also of importance with regard to chronic LNB, for which the same associations have been demonstrated [295 - 298].

The extrapulmonary manifestations frequently extend across a long period of time, i.e. across months and years. This also applies to the so-called reactive arthritis, whose differentiation from the arthritides in Lyme disease is sometimes difficult. Attention should also be paid to the Guillain-Barré syndrome which can last for months and presents in the same manner as in the Lyme disease. The association with a myocarditis is also similar, whereas meningoencephalitis occurs in the acute phase, i.e. practically simultaneously with pneumonia.

The laboratory diagnostics for Chlamydophila pneumoniae includes serology, the lymphocyte transformation test (LTT), and the detection of the pathogenic organism using PCR (Tab. 12):

Table 12
Laboratory diagnostics for Chlamydophila pneumoniae

- Serology
- Lymphocyte transformation test (LTT)
- Detection of pathogen (PCR)

The serology results have severe inherent limitations. There is a considerable discrepancy between the serological findings, on the one hand, and pathogen detection using PCR, on the other hand [135, 136].

A single test for IgG has only a very low sensitivity [137], whereas the sensitivity is quite good in cases of a definite increase in IgG between the acute phase and the further course of the disease.

The diagnostic value of LTT for Chlamydophila pneumoniae has not yet been validated in the literature.

The chronic disease course obviously represents a chronic persistent infection. Chlamydophila pneumoniae could be detected both in the synovial fluid and in the liquor using PCR [234, 235, 236, 239, 240].

The antibiotic treatment of Chlamydophila pneumoniae is given in Table 13. The drug of choice is doxycycline; macrolides also exhibit good efficacy, particularly azithormycin; quinolones have a low efficacy [138]. However, gemifloxacin has proven to be very effective [242].

Table 13
Antibiotic treatment of Chlamydophila pneumoniae

Antibiotic	Dose / Day
Azithormycin	500 mg
Clarithromycin	1000 mg
Telithromycin	800 mg
Doxycycline	400 mg
Gemifloxacin	320 mg
Rifampicin (in combination with doxycycline or azithormycin)	600 mg
Treatment duration for chronic course (no reliable data basis):	2 - 3 months, if necessary 6 months for so-called reactive arthritis [234]

Chlamydia *trachomatis*

The microbiological anomaly of Chlamydia was presented in the chapter "Chlamyophila pneumoniae". With regard to the antibiotic treatment, the fact that Chlamydia are present in their infectious form both intracellularly and extracellularly is decisive.

Chlamydia trachomatis is sexually transmitted and causes a urogenital infection. The differential diagnostic reference to Lyme disease results primarily from the arthritides, which are caused by a chronic persistent infection in both diseases. In Chlamydia trachomatis, the arthritis is assigned to the so-called reactive arthritis even though the detection of the pathogen occurred in the synovial fluid in studies [243, 244].

The arthritis occurs in 1% of the urethritis induced by Chlamydia trachomatis. Reiter's triad (arthritis, uveitis, urethritis) occurs in 0.3% of those affected.

The disease can be easily detected by means of laboratory diagnostics (cf. Tab. 14) in cases of existing urogenital infection. In this context, NAATs (nucleic acid amplification techniques) in urethral smear or in urine are available; this examination is also reliable for asymptomatic patients [140-142]. PCR also has a high sensitivity and specificity [143].

Table 14
Laboratory diagnostics for Chlamydia trachomatis

- NAATs
- PCR (detection of pathogen)
- Serology
- LTT*

*diagnostic value has not been validated

The diagnostic value of serology and LTT has not been validated. Moreover, whether a chronic infection with Chlamydia trachomatis (as is the case with LD) can be accompanied by seronegativity has not been clarified. Seropositivity can indeed provide evidence of a previous infection, but principally does not allow any statement with regard to a disorder as a consequence of a persistent infection with Chlamydia trachomatis. Theoretically, a persistent or reproducible pathological lymphocyte transformation test indicates a prolonged infection, but scientific data for the diagnostic value are not yet available.

The significant data on the mode of transmission, symptomatology and treatment are summarized in Table 15.

Table 15
Chlamydia *trachomatis*
Infection data, symptomatology, treatment

Pathogen:

- Chlamydia *trachomatis*

Transmission:

- sexual

Symptomatology:

- Arthritis
  (so-called reactive arthritis
  actually persistent infectious arthritis)

- Reiter's triad
  Arthritis
  Urethritis
  Uveitis

Treatment

- as in Chlamydophila pneumoniae
  (see Tab. 13, page 19)

Duration of treatment

- 3 months [234] or longer
- Sulfasalazine [224],
  TNF antibodies [225]

Yersinia enterocolitica infection (yersiniosis)

In the differential diagnosis of Lyme disease and with regard to coinfection, the importance of yersiniosis is primarily based on the disease manifestation of a so-called reactive arthritis. As in Chlamydia infections and probably also in the bartonellosis, the arthritis is very probably the consequence of a chronic persistent infection [163, 164]. Since the so-called reactive arthritis in yersiniosis occasionally also occurs in the scope of Reiter's triad, i.e. in connection with urethritis and uveitis, the autoimmune processes are to be discussed with the pathophysiology. The thyroiditis which frequently occurs in yersiniosis and which is very probably expression of an autoimmune phenomenon as in LD is indicative of such an association.

The anamnestic research subsequent to the early phase of yersiniosis makes an important contribution to the recognition of chronic yersiniosis. The early phase of yersiniosis is essentially characterized by two disease manifestations:

- Gradually beginning gastroenteritis
- Pharyngitis

The infection data and symptomatology of yersiniosis are compiled in Table 16.

Table 16
Yersiniosis (Y. enterocolitica)
Infection data, symptomatology

Pathogen:

- Yersinia enterocolitica

Transmission:

- Fecal-oral

Reservoir:

- Various vertebrates

Early phase:

- Gradual development of gastroenteritis (for about one week)
- Gastroenteritis
- Pharyngitis
- Complications due to inflammation of the intestinal wall
- Mesenteric lymphadenopathy
- Pathogen localization in lymphatic tissue of the pharyngeal wall
- Pathogen detection by means of a throat swab
- Excretor (months after the abatement of the gastroenteritis

Late phase:

- Reactive arthritis
- Erythema nodosum
- Arthralgias
- Ankylosing spondylitis
- Rheumatoid arthritis
- Sacroiliitis
- Iridocyclitis
- Abdominal pains
- Diarrhea
- Ulcerative colitis
- Neurological disease manifestations
  (central, peripheral)
- Nephritis
- Diabetes mellitus (insulin-dependent)
- Hepatitis
- (ANA positive)
- (Rheumatoid factor positive)
- Multisystem disease
- Reduction of the overall survival time
- (thyroiditis)
- Pathogen detection in articular effusion
- Pathogen detection in blood
- Disease progresses in stages and intervals with fewer complaints
- Correlation with thyroiditis
- Positive LTT
- Oscillating serological findings
  (correlation with disease expression)
- (Erythema nodosum)
- (Conjunctivitis)
- (Gastrointestinal complaints)
- (seldom: myocarditis)

Articular manifestations:

- Hip joints
- Knee joints
- Upper ankle joint
- Sacroiliac joints

Yersinia enterocolitica was already recognized as pathogen as early as the beginning of the 20th century. However, the true significance of the pathogen, in particular, under epidemiological aspects was first described in 1995 [146].

Acute illness due to Y. enterocolitica is subject to registration (according to German law).

The pathogen penetrates into the intestinal wall and the mesenteric lymph nodes. Surface proteins and plasmid-bound virulence factors suppress the immune system of the host organism [147-150].

The disease results primarily in gastroenteritis, pseudoappendicitis, und mesenteric lymphadenitis.

In contrast to other bacterial gastroenteritides, the Yersinia enterocolitic gastroenteritis develops gradually and often becomes stressful or perceivable only after a week has passed [15 - 153]. Frequently, the infection is associated with a pharyngitis because the pathogens remain in the lymphatic tissue of the tonsils and the pharyngeal wall, where they can also be detected by means of a smear test. The concurrent occurrence of gastroenteritis with pharyngitis is typical for a yersiniosis [154].

The mean disease duration is approximately two to three weeks, but distinctly longer diseases courses have been described. The acute illness can be associated with numerous gastrointestinal complications, primarily as a consequence of a severe bacterial inflammation of the intestinal wall [155-157]. In addition, the disease can also affect many non-gastrointestinal organs [155, 156, 158 - 161].

The patients frequently remain excretory for months, even when the gastroenteritis has long since abated [152].

The yersiniosis can result in so-called reactive arthritis and is thus an important infectious disease in the differential diagnosis of Lyme disease. Since the disease can also sporadically occur [152] and frequently remains unrecognized, the anamnestic research for typical yersiniosis disease manifestations and data is of considerable importance, particularly in the early phase.

Differentiation between LD and yersiniosis is made even more difficult by the fact that both infections can cause a multisystem disease. For information on the individual disease manifestations see Table 16.

The study by Saebo und Lassen [246], which determined many disease manifestations in a retrospective study of 458 patients, is of particular importance for the depiction of chronic yersiniosis: chronic persistent arthralgias, ankylosing spondylitis, rheumatoid arthritis, iridocyclitis, chronic abdominal pains, chronic diarrhea, ulcerative colitis, nervous disorders, nephritis, thyroid disorders, insulin-dependent Diabetes mellitus, chronic hepatitis, (multisystem diseases) and a substantial reduction of the overall life expectancy. Many of the individual relationships were depicted in further publications by these authors [252 - 256, 257].

Studies which immediately suggest a possible relationship between Yersinia and inflammatory intestinal disorders [257] close the pathophysiological circle between Yersinia, inflammatory intestinal disorders and enteropathic arthritides.

Despite this, it should be noted that the relationship between Yersinia infection and the above-mentioned numerous disease manifestations (except for arthritis) have been inadequately analyzed. This may be due to the fact that yersiniosis' significance as a disease has only been recently recognized.

The so-called reactive arthritis primarily affects the hip, knee and upper ankle joints as well as the sacroiliac joints; occasionally there are additionally chronic pains in the lumbosacral region [165]. This arthritis can last for months, and exhibit recurrent and symptom-free intervals in the disease course. — The so-called reactive arthritis in yersiniosis can occur alone, but occasionally also in connection with conjunctivitis and urethritis (previously termed Reiter's syndrome [162]).

In the differential diagnosis of Lyme disease, it is of particular interest that the pathogen (Y. enterocolitica) could be detected in articular effusions in studies of the so-called reactive arthritis [163, 164].

Sometimes these arthritides last for many years. In addition, there is a relationship between yersiniosis and thyroiditis. All these facts (chronic arthritides, multisystem disorders, disease course lasting for years, correlation with regard to thyroiditis) can be observed in the same manner in Lyme disease. Thus, the differential diagnosis is sometimes extremely difficult.

The laboratory diagnostics of Yersinia enterocolitica infection is presented in Table 17.

Table 17
Laboratory diagnostics of Yersinia enterocolitica infection

Serology
LTT*
Pathogen detection
- PCR
- Culture

As is the case in Lyme disease, there is often seropositivity in non-diseased people Information on a possible seronegativity in chronic yersiniosis is not available.

In the disease course the serological findings can correlate with the disease expression [165].

It is not at all seldom that a highly significant pathological Yersinia LTT is found in patients whose complaint symptomatology is primarily consistent with chronic Lyme disease. In correspondence to chronic Lyme disease, the positive yersinia LTT could be an indication of a chronic persistent infection especially in cases involving reproducibility.

The focuses which are to be considered in the differential diagnosis of chronic Lyme disease or chronic yersiniosis, respectively, are depicted in Table 16.

Pathogen detection is particularly possible in articular effusion as well as in the lymphatic tissue of the intestine as well as in early stages also by means of a throat swab. Data on the sensitivity of pathogen detection using PCR or culture methods does not exist in the relevant literature.

In Yersinia-PCR-positive patients, the serology was positive in 70% of the cases; the LTT in 50% [248].

In the initial detection of Yersinia enterocolitica using culture methods, IgA and IgG bands were found in immunoblot assay in patents experiencing a chronic course. The continuous detection of IgA antibodies was obviously an expression of a persistent infection; in this context the pathogens were detected in the intestinal mucosa and in lymphatic tissue. Hence, this was a definitely chronic, persistent Yersinia enterocolitica infection [258]. The antibiotic treatment of the Yersinia enterocolitica infection is presented in Table 18.

Table 18
Antibiotic treatment of the Yersinia enterocolitica infection

Antibiotic	Dose / Day
Ceftriaxone + Gentamycin	2 g 240 mg
Ciprofloxacin	1000 mg
Trimethoprim and sulfamethoxazole	875 / 125 2 x daily
In accordance with test:	
Gentamycin Doxycycline Piperacillin Invanz	240 mg 400 mg 8 g 1 g

Yersiniosis frequently abates within a few weeks so that an antibiotic treatment is not generally recommended. This also applies with regard to the excretors. Only in cases of severe disease courses, in particular with sepsis, are antibiotics used.

Y. enterocolitica produces beta-lactamases with the consequence that penicillin, ampicillin and the cephalosporins of the first generation are ineffective [201, 205]. There is also frequently a resistance to macrolides.

It is also disputed whether early antibiotic treatment (i.e. for gastroenteritis) prevents reactive arthritis [203].

The differential diagnosis of chronic yersiniosis or chronic Lyme disease, respectively, is thus as a consequence of the many instances of overlap in the symptomology extremely difficult. In cases in which both diseases are present in their chronic form, a differentiation is often not possible at all.

Mycoplasma pneumoniae infection

The differential diagnostic differentiation between LD und Mycoplasma pneumoniae infection or the recognition of the coinfection by Mycoplasma pneumoniae is problematical because both diseases exhibit many identical disease manifestations; this applies to the extrapulmonary manifestation in Mycoplasma pneumoniae infections: disorders of the CNS, of the musculoskeletal system, of the heart, of the kidney and of the eye.

The infection data and the symptomatology are given in Table 19. In the foreground is the atypical pneumonia, frequently linked to symptoms in the region of the upper respiratory tract. There is no data on the frequency of extrapulmonary manifestations in the literature.

Table 19
Mycoplasma pneumoniae infection
Infection data, symptomatology

Pathogen:

Mycoplasma pneumoniae

Transmission:

Droplet infection, humans

Pulmonary symptomatology (and attendant symptoms):

- (above all older people in nursing and old people’s homes are affected)
- Incubation period 3 weeks
- Atypical pneumonia (3% - 10% of the cases.)
- Bronchitis
- Pharyngitis
- Rhinitis
- Earaches
- Sinusitis

Extrapulmonary manifestations:

- Maculopapular exanthema
- Vesicular dermatitis
- Disorders in CNS (rare:
  - Encephalitis
  - Meningitis
  - Myelitis
  - Cranial neuropathy
  - Cerebellar ataxia

Gastrointestinal symptoms:

- Hepatitis
- Pancreatitis

Rheumatic symptoms:

- Arthritis
  - Arthralgias
  - Myalgias
  - Polyarthritis

Cardiac symptoms:

- Cardiac arrhythmias
- Atrioventricular blockMyocarditis

Glumerulonephritis

Uveitis

Mycoplasma pneumoniae is considered to be the most important pathogen of atypical pneumonia. However, pneumonia only occurs in approximately 3% - 10% of the cases in Mycoplasma pneumoniae infections [204]. In most cases, the infection results in a banal bronchitis [204], pharyngitis, rhinitis, ear aches, and sinusitis [205].

All the extrapulmonary disease manifestations listed in Table 17 are seldom [206 - 214]. In arthritis, Mycoplasma pneumoniae was detected in the synovial fluid by means of PCR [211]; this is an indication of a direct relationship to the infection.

Pathogen detection in articular effusion and the many extrapulmonary disease manifestations document the chronic disease course in cases of Mycoplasma pneumoniae. However, precise data on the chronic disease course are not available in the literature In particular, whether a chronic infection, especially with extrapulmonary disease manifestation, can persist with seronegativity is unclear. Seropositivity documents the infection, but it principally cannot serve as a diagnosis basis for a chronic persistent Mycoplasma pneumoniae infection.

The literature on the relationship between Mycoplasma pneumoniae and neurological disease manifestations is comparatively extensive. The publications primarily refer to neurological complications in pneumonia, i.e. the early phase of the Mycoplasma pneumoniae infection.

The neurological manifestations involve both the early phase, i.e. the point in time of existing pneumonia due to Mycoplasma pneumoniae, and later disease stages. Changes in the region of the brain stem [259, 267], myelitis [260, 263, 265, 269, 271, 274, 277, 279, 281, 284, 286], Guillain-Barré syndrome [261, 262, 268, 272, 282, 283], encephalitis [270, 273, 275, 276, 278, 280, 281, 285, 286], meningitis [270], polyradiculopathy [263], peripheral facial paresis [264, 266], optical neuritis and hemorrhagic leukoencephalitis [268], peripheral polyneuropathy [270], disorders of the brain nerves [282], radiculitis [282] have been described.

The frequency of neurological symptoms in connection with Mycoplasma pneumoniae varies between 1‰ [287], 1% [288], and 5% [289]. The pathogen has been repeatedly detected by means of culture methods or PCR [270, 274, 283].

Pathogen detection in serum and liquor is considered to be proof that the neurological manifestations are mediated infectiously and not immunologically [283]. However, the connection between Mp and neurological manifestations is not undisputed [290, 287].

Other extrapulmonary manifestations mentioned in the literature involve hepatitis, hemolytic anemia, Schönlein-Henoch purpura, disorders of the muscular-skeletal system, of the skin and other organs [265], macula edema [270], bilateral uveitis [291], nephritis [292], arthritis, hepatitis, pericarditis [292].

The laboratory diagnostics for Mycoplasma pneumoniae is presented in Table 20. The serology only becomes positive after several weeks, as is the case for most infectious diseases. It is therefore significant for the chronic disease course. Seropositivity substantiates the infection, but not the disease. Whether a chronic infection can also exist in cases of seronegativity has not yet been scientifically clarified.

The LTT for Mycoplasma pneumoniae has not been validated by studies.

Pathogen detection, e.g. in articular effusion is possible, but it is difficult, has a low sensitivity and is therefore not part of routine diagnostics.

Table 20
Laboratory diagnostics for Mycoplasma pneumoniae infection

Serology
LTT
Pathogen detection
- PCR
- Culture

The antibiotic treatment of Mycoplasma pneumoniae is presented in Table 21. The drugs of choice are azithormycin [293] und levofloxacin [294].

Table 21
Antibiotic treatment of Mycoplasma pneumoniae infection

Antibiotic	Dose / Day
Azithormycin	500 mg
Levofloxacin	500 mg
Doxycycline	400 mg

Secondary coinfections of Lyme disease

In the following, additional infections will be presented, which are mentioned in international publications as coinfections of Lyme disease—in particular HGA (human granulocytic anaplasmosis) and babesiosis. These two coinfections are of importance in the USA, but not in Europe.

Because of the similarity of their symptoms to those of LD, the following diseases are included for completeness' sake: tularemia, Q fever, parvovirus B19 infection and Campylobacter jejuni infection.

Human granulocytic anaplasmosis (HGA)

Human granulocytic anaplasmosis (Synonym: Human granulocytic ehrlichiosis (HGE)) is transmitted by ticks. Its reservoirs are red deer and the white-footed mouse The HGA pathogen can be simultaneously transmitted with Borrelia burgdorferi with the consequence of a double infection. HGA exhibits many symptoms which also occur in the same form in LD. Indications of HGA are pathological laboratory findings in the form of leukopenia, thrombocytopenia, and elevated transaminases.

The pathogen is localized intracellularly. The transmission to mice has been proven [193].

In connection with ehrlichiosis or anaplasmosis, respectively, two pathogens are to be noted:

- Ehrlichia chaffeensis [1]
- Anaplasma phagocytophilum [2]

E. chaffeensis infects monocytes; A. Phagocytophila, granulocytes.

E. chaffeensis is the pathogen of human monocytic ehrlichiosis (HME), a very rare infectious disease, which occurs primarily in the USA and some regions of South America, but practically nowhere else on earth.

E. phagocytophila is the pathogen of human granulocytic anaplasmosis, another extremely rare disease in the USA with an annual incidence of approximately 10 / 1 million in habitants [3].

The infection data and symptomatology are compiled in Table 22.

Table 22
Human granulocytic anaplasmosis (HGA)
Infection data, symptomatology, treatment

Pathogen:

- E. chaffeensis and Anaplasma phagocytophilum

Transmission:

- Ticks (I. ricinus (Europe), I. scapularis (USA))

Reservoirs:

- Red deer, human beings (E. chaffeensis). White-footed mice (Anaplasma phagocytophilum)

Intracellular localization

Symptomatology:

- Fever
- Influenza-like symptoms
- Headaches
- Joint pains
- Muscle pains
- Coughing
- CNS disorders
- Meningitis

Pathological laboratory findings:

- Leukopenia
- Thrombocytopenia
- Elevated transaminases
- Anemia (rare)
- Elevated creatinine (rare)

Treatment:

- Doxycycline

The pathological importance of human monocytic ehrlichiosis (HME) and human granulocytic anaplasmosis (HGA) was discovered in 1986 and 1994, respectively [35, 36]. The two infectious diseases resemble each other clinically and with regard to laboratory findings.

The pathogens develop in monocytes (HME) or in granulocytic leukocytes (HGA). Thus, their localization is exclusively intracellular.

The pathogens are transmitted by ticks, in the United States primarily via Ixodes scapularis, in Europe, via I. ricinus.

Important reservoirs: deer (HME); wood mice (HGA) In addition, other modes of transmission are being discussed: mother-child transmission, blood transfusions, direct contact with infected animals, transmission form person to person [37, 38, 41, 42, 43, 44].

Scientific reports on illnesses due to HGA in Europe are rarities [4]. However, studies in Northern Italy showed that 24% of the ticks (I. ricinus) were infected by E. chaffeensis or A. phagocytophilum. Similar figures have been substantiated in the Netherlands and in Poland, whereas in Germany they are at approximately 2% [5 - 10]. The figures for the East Coast of the United States were higher; approximately of the order of 30% - 40% [11, 12].

In patients with Lyme disease the seroprevalence for A. phagocytophilum in Europe is approximately 10% [13 - 15]. Similar figures were also obtained in the USA [16].

Since seroprevalence merely expresses something about the frequency of the infection, but nothing about the disease (HGA), no reliable statements about the frequency of the disease (prevalence of HGA) can be made. According to the laws of probability, a concurrent HGA infection in patients with Lyme disease might amount to a few percent at most.

There is no literature on chronic HGA courses. However, subacute and chronic courses are discussed [17, 19].

The incubation period, i.e. the time between the tick bite and emergence of the acute illness, is approximately one week on average [18].

The laboratory diagnostics for HGA is presented in Table 23. As mentioned above, HGA is characterized by leukopenia, thrombocytopenia, and elevated transaminases. Such changes occur frequently and are—particularly in cases involving a febrile clinical picture with the above-mentioned symptoms (Tab. 22)—an indication for HGA. Verification of the infection is performed using serology, other methods of detection, particularly direct pathogen detection, are not often successful and therefore are not part of the routine diagnostic methods.

The determination of HGA (also as coinfection) merely on the basis of serological findings is dubious since seropositivity does not verify the presence of the disease (HGA), but only the prior infection. Also in the case of HGA, the diagnosis is based primarily on the totality of anamnesis, physical examination findings, medicinal-technical findings, and differential diagnosis.

Table 23
Laboratory diagnostics for HGA

- In the acute phase clusters of bacteria intercellular (morulae) [20]
- PCR from whole blood
- Serology [45-48]
- (Occurrence of antibodies two to three weeks after disease onset, prolonged persistence after abatement of the disease)
- Detection in blood smear [49-52]
- Detection in 20% - 80% of the cases by means of PCR
- (Sensitivity of PCR 60% - 80% [53-56])

Doxycycline is recommended as therapy, also for children. Precise literature with regard to an adequate treatment is not available.

In summary, it can be stated that HGA as individual disease and as so-called coinfection in cases of Lyme disease is not of major importance in Europe; however, the literature in this problem complex is currently completely inadequate.

Babesiosis

Pathogens: Babesia microti, Babesia divergens [57, 58]
Vector: ticks (I. ricinus (Europe), I. scapularis (USA)) [57, 58]
Other modes of transmission: blood transfusions [59], perinatal [60, 61]
Reservoir: cattle (other vertebrates)

Laboratory diagnostics:

- Detection in blood smear (difficult, repetition frequently required)
- PCR (higher sensitivity than blood smear [62])
- Serology [63, 64]
- Poor correlation between serologic titer and symptomatology [64]

Babesia are protozoa and result in lysis subsequent to invasion of erythrocytes.

Two species of Babesia are pathogenetically significant.

- Babesia microti
- Babesia divergens

B. microti is the predominant pathogen in the USA; B. divergens, in Europe [cf. 196]. The transmission of the pathogen occurs primarily via ticks. B. microti has been found as a coinfection in LD [197, 198, 199].

Since 1956 a total of only 30 cases has been reported in Europe. The majority of these patients were splenectomized.

The prevalence of B. microti and B. divergens in ticks is 10% - 20% in Europe [21 - 23], in the USA, sometimes higher [24].

The seroprevalence with regard to B. microti and B. divergens is 0% in patients with Lyme disease [25, 26] and thus is in stark contrast with the frequency of the pathogen in ticks.

The situation in the USA is different: there the seroprevalence is approximately 10% - 20% [27 - 30]. In the USA instances of the disease are reported correspondingly more frequently, in some cases with severe disease courses [31 - 34]. This difference can obviously be only explained by the fact that B. microti, the predominant pathogen in the USA, has a very much higher virulence than B. divergens.

Thus, Babesiosis dos not play a major role in Europe unless the patient contracted the disease in a foreign country, e.g. in the USA.

The clinical picture presents as a febrile, influenza-like medical condition with chills and fever, arthralgias, myalgias, and gastrointestinal symptoms. Severe disease courses only occur in non-immunocompetent patients.

The treatment is carried out with atovaquone, azithormycin, clindamycin, if necessary in combination with quinine.

By means of the assessment of all data, it can be determined that babesiosis—due to the dominant European pathogen, B. divergens—does not represent a major health hazard and thus is of little consequence as a coinfection in cases of Lyme disease.

Rickettsioses

To begin with, attention should be directed to the fact that the bartonellosis pathogen belongs to the Rickettsia family.

In the USA the most important rickettsiosis is Rocky Mountain Spotted Fever (RMSF), a potentially fatal, but normally curable disease. RMSF is the most frequent rickettsiosis in the USA. The clinical picture is primarily characterized by high fever, pronounced malaise, abdominal complaints, and a generalized exanthema. Occasionally, the disease is also linked with CNS manifestations (focal neurological deficits, cerebral seizures):

Worldwide, there are many different rickettsioses, which are caused by different Rickettsia subspecies. The transmission generally occurs via ticks, but also via mites, fleas, and lice. Generalized exanthema—the so-called localized eschar (black wound)—as well as fever, headaches and severe muscle pains are typical symptoms of the disease.

The most important rickettsiosis in Europe is the Mediterranean spotted fever; pathogen: R. conorii. The disease primarily affects Southern Europe.

Treatment is performed with doxycycline.

Chronic courses have not been described in the literature. Differential diagnostic problems in comparison to Lyme disease in the early stage should not result because of the endemic circumstances and the presence of the exanthema.

For further information refer to the relevant medical literature.

Tularemia

Tularemia is caused by the pathogen Francisella tularensis. Transmission occurs via mosquitos. The disease reservoir comprises many vertebrates.
Main disease manifestations: fever, headaches, malaise, swollen lymph nodes, pharyngitis, eschar (black wound), emesis, pneumonia, erythematosus papular-ulterative lesion at the location of the bite with black spot (central eschar, “tache noire”).

Treatment: tetracyclines, ciprofloxacin.

Betalactamases are ineffectual.

Relapses can occur; persistent chronic courses have not been described in the relevant literature. In the differential diagnosis problems can occasionally occur in the early stage in cases lacking erythema migrans in comparison with Lyme disease.

For further information refer to the relevant medical literature.

Q fever

In contrast to rickettsioses (Mediterranean fever) and tularemia, Q fever can exhibit a chronic course. With regard to the symptomatology, however, there are no significant differential diagnostic problems with regard to Lyme disease.

Q fever occurs normally endemically and as a rule is caused by contact with livestock via inhalation or oral transmission of the pathogen. Admittedly, C. burnetii can also be found in other reservoirs, e.g. in ticks, but two items are decisive for the diagnosis:

- Endemic occurrence
- Contact with (diseased) livestock and their products (milk products)

The decisive diagnostic information with regard to a possible Q fever is thus the occupational activity or the contact with agriculture and livestock. In sporadic cases can the frequent consumption of raw milk or the contact with diseased cattle (abort) be an indication of an infection hazard.

Significant disease manifestations:

- Transitory influenza-like clinical picture
- Pneumonia
- Hepatitis
- Other manifestations:

- Erythema
- Pericarditis / Myocarditis
- Meningitis / Encephalitis [318-320]
- Myelitis [316, 317]

The chronic course of Q fever can persist for months or years. In this context, chronic endocarditis is the dominant disease manifestation.

Disease manifestation in cases of chronic course:

- endocarditis, pericarditis, Guillain-Barré syndrome [315]

The diagnosis is normally verified by the occurrence of antibodies, i.e. thus by means of serological tests.

For further information refer to the relevant medical literature.

Human parvovirus B19 infection

Pathogen: human parvovirus B19
Transmission: respiratory tract (droplet infection)
Transmission during pregnancy
Blood transfusion

Reservoir: human beings

The disease can exhibit a chronic course, i.e. over months and years [171]. Whether parvovirus B19 causes chronic myocarditis and cardiomyopathy is a matter of dispute [172-175]. The chronic course is verified by means of pathogen detection in articular effusion, myocardium, bone marrow, and blood [169-175].

With regard to Lyme disease, the following differential diagnostic disease manifestations are relevant:

- Persistent or recurrent arthropathy
- Myocarditis
- Cardiomyopathy

Fifth disease (erythema infectiosum) is a typical skin manifestation of a parvovirus B19 infection in children, but does not normally occur in adults. Arthralgias can last for months or years.

For further information refer to the relevant medical literature.

Campylobacter jejuni

Campylobacter jejuni (Cj) is a small gram-negative bacterium whose pathological significance was recognized in the 1980s. Worldwide, Cj is among the most frequent pathogens causing acute diarrhea Sources of infection are game animals and domestic animals, animal products and especially poultry [299]. The pathogen can persist in a coccoid form, but also in its normal form, for months in cases of unfavorable living conditions. It penetrates into the epithelial cells of the intestine and causes their destruction, possibly by means of toxins [303, 304].

The main manifestation of the Campylobacter jejuni infection is gastroenteritis. In the early phase (gastroenteritis), complications can occur in the abdominal region.

Cj has differential diagnostic significance due to complications in the late stage: reactive arthritis, Guillain-Barré syndrome.

Reactive arthritis in Cj infections is seldom; its frequency amounts to a maximum of 2.6% [305 - 308]. In connection with a Cj infection, the Guillain-Barré syndrome has a comparatively unfavorable prognosis [309]. Its incidence amounts to approximately 1‰ [310].

Reactive arthritis occurs approximately one to two weeks after gastroenteritis [304]; Guillain-Barré syndrome, in a period approximately two months after onset of infection [311].

The infection data and symptomatology are compiled in Table 24.

Antibiotic treatment reduces the duration of gastroenteritis. Macrolides [312] and quinolones are primarily recommended, but resistances to them can also occur [313]. Resistance to trimethoprim und beta-lactamases exists [314].

Table 24
Campylobacter jejuni infection
Infection data, symptomatology, treatment

Pathogen:

- Campylobacter jejuni

Transmission:

- Fecal-oral

Sources of infection:

- Game and domestic animals
- Particularly poultry
- Animal products
- (contaminated water)

Symptomatology:

- Early phase:
  - Gastroenteritis
  - (abdominal complications)

- Late phase:
  - Reactive arthritis
  - Guillain-Baré syndrome

Antibiotic treatment:

- Erythromycin 1500 mg
- Azithormycin 500 mg daily
- Ciprofloxacin 1000 mg daily

Reactive arthritis

The term “reactive arthritis” characterizes arthritides which bear a relationship to certain infectious diseases. In former times the term “Reiter syndrome” was used in cases of concurrent infection of the urethra and the uvea. Arthritis, urethritis and uveitis were termed Reiter’s triad [215, 216]. Infectious diseases which can induce reactive arthritis are given in Table 25.

Table 25
Pathogens in association
to reactive arthritis

Chlamydia *trachomatis*
Chlamydia pneumoniae
Yersinia enterocolitica
Salmonellae
Shigella
Campylobacter
(usually C. jejuni)
Mycoplasma pneumoniae

Possibly:
Clostridium difficile

The term “reactive arthritis” is not a defined disease (nosological entity), but rather a concept for the classification of disease relationships and of the pathophysiology.

The term “reactive arthritis” is problematical because in many infections the pathogens were detected in the synovia and joint fluid in cases of such so-called reactive arthritis. This is true for Chlamydophila pneumoniae [234-236], Chlamydia trachomatis [243, 244] and for Yersinia enterocolitica [163, 164]. — Moreover, the pathogen was also found in the synovia in cases of arthritides in connection with Mycoplasma pneumoniae [211].

Reactive arthritis occurs days to weeks after the onset of infection. It predominantly affects the joints of the lower extremities. In cases involving a disease duration of less than 6 months, the term “acute reactive arthritis” was selected, for disease duration of more than 6 months, the term “chronic reactive arthritis" is used.

In 50% of the cases, joints of the upper extremities are also affected, including the small joints, and the arthritis can be accompanied by cases of tendonitis (enthesitis) [217 - 219, 220].

One of the most important differential diagnoses of reactive arthritis is Lyme arthritis (chronic Lyme disease, Lyme disease in the late stage, stage III).

Reactive arthritis can be associated with other disease manifestations; they are presented in Table 26.

Table 26
Extra-articular symptoms in cases of reactive arthritis

Urogenital symptoms
Conjunctivitis
Uveitis
Aphthae
Hyperkeratotic skin changes in the region of the sole of the foot and the palm of the hand
Nail changes as in psoriasis
Genital lesions, e.g. balanitis

In the diagnosis of a “reactive arthritis” anamnestic research is to be performed to determine whether there are indications of one of the above-mentioned infections. Accordingly, the following significant anamnestic aspects result:

- Chlamydia trachomatis infection
  (with and without symptoms)
- Enteritis
- Atypical pneumonia

Additionally, it should be remembered that arthritides also are found in Chlamydophila pneumoniae und Mycoplasma pneumoniae; and that in Chlamydioses, Yersiniosis and also in cases of Mycoplasma pneumoniae, the pathogen has been detected in the synovial fluid or in the articular effusion, respectively.

Using laboratory tests (culture, serology), an existing or previous infection can be detected in 50% of the cases. Other laboratory tests, particularly so-called inflammation markers (BSG, CRP, leukocytosis) are not relevant in cases involving reactive arthritis.

With regard to Chlamydia trachomatis, pathogen detection in a urethral smear or in urine using PCR is appropriate.

Chronic courses, i.e. a duration of illness exceeding 6 months, are observed in nearly 20% of the patients [222].

NSAIDs are used for treatment, but only for pain relief since they have no influence on the disease course or disease duration. In contrast, sulfasalazines [224] and TNF antibodies develop a certain efficacy.

An antibiotic treatment is recommended in cases of acute chlamydiosis with the objective of reducing the frequency of reactive arthritis. However, corresponding studies are not available [223]. In cases of chronic reactive arthritis, the findings on the efficacy of an antibiotic treatment are a matter of controversy [220, 226, 227 - 231].

Overview of the symptomatology and treatment of LD and chronic coinfections

An informative overview of the different disease manifestations of LD and the significant coinfections is given in Table 27. The overview shows than there is substantial symptom overlap in cases of LD, bartonellosis, Y. enterocolitica and Mycoplasma pneumoniae. Additionally, Chlamydophila pneumoniae also exhibits some overlap in the symptomatology. Chlamydia trachomatis and Campylobacter jejuni are primarily characterized by reactive arthritis and the rare Guillain-Barré syndrome. Only in cases of chronic Lyme disease does the antibiotic treatment (Table 28) involve the use of cephalosporins of the 3rd generation and, if necessary, of carbapenems. Otherwise, the focus is generally on the tetracyclines, the macrolides, to some extent on the quinolones, particularly gemifloxacin; all of which exhibit an intracellular and extracellular efficacy.

Table 27
Disease manifestations of chronic LD and chronic coinfections (overview)

Disease	Symptomatology:									
	GenS	MuSk	NS	Skin LA	Heart	Eye	GI	UG	rA	GBS
LD	+	+	+	+	+	+	+	+	(+)*	+
Bartonellosis	+	+	+	+	+	+	+	+	+	+
Y. enterocolitica	(+)	+	+	+	+	+	+		+	
Mycoplasma p.	(+)	+	+	+	+	+	+	+	+	+
Chlam. p.			+		+				+	+
Chlam. tr.						+			+	+
Campylobacter jej.									+	+

GenS	General symptoms	(fatigue, head aches, lassitude)
MuSk	MusculoskeletalDis.	(arthritis, arthralgias, myalgias)
NS	Nervous system	(CNS, polyneuropathy, radiculopathy)
Skin	EM, ACA in cases of LD	(e.g. infected skin injury)
LA	Lymphadenopathy	(lymphadenopathy in cases of bartonellosis)
Heart		(myocarditis, cardiomyopathy, pericarditis)
Eye		(uveitis, conjunctivitis, optic neuritis)
GI	Gastrointestinal complaints	
UG	Urogenital disorder	
rA	Reactive arthritis	
GBS	Guillain-Baré syndrome	

(+) Presumption based on general symptoms in cases of yersiniosis and Mycoplasma pneumoniae infection

(+)* Probably chronic infectious, hypothetical autoimmune (mimicry)

Table 28
Antibiotic treatment of chronic LD and chronic coinfections

Disease	Antibiotic						
	Ceph3	Carbap	Tetracyc	Macrol	Quinol	TMSU	Rifa
LD	+	+	+	+	+ (Gemifloxacin)		
Bartonellosis			+	+	+	+	+
Y. enterocolitica	+	+	+				
Mycoplasma p.			+	+	+		
Chlam. p.			+	+	+ (Gemifloxacin)		+
Chlam. tr.			+	+	+ (Gemifloxacin)		+
Campylobacter jej.				+ (Erythromycin)	+		

- Ceph3 (if necessary + gentamycin)
- subsequent to Testing: Piperacillin

Ceph3	(3rd generation cephalosporins)
Carbap	(Carbapenems)
Tetracyc	(Tetracyclines)
Macrol	(Macrolides)
Quinol	(Quinolones)
TMSU	Trimethoprim and sulfamethoxazole
Rifa	Rifampicin

Conclusion

At the end of the 20th century, a number of infectious diseases attracted the attention of medical and health policy interests. This is primarily due to the fact these diseases frequently have a chronic course. In Europe and North America, but also in many other areas of the world, these chronic diseases are caused by the following pathogens: Borrelia burgdorferi, Bartonella henselae, Mycoplasma pneumoniae, Chlamydophila pneumoniae, Chlamydia trachomatis, Yersinia enterocolitica. In North America, HGA (Human Granulocytic Anaplasma) and Babesias are also important, whereas infections with these pathogens are a rarity in Europe. In addition, other pathogens discussed in the text are of secondary importance with regard to their frequency of occurrence. Borrelia burgdorferi is transmitted by ticks; in some cases this also applies to Bartonella henselae. The two diseases can also be simultaneously transmitted by tick bites. The remaining pathogens mentioned have other modes of transmission. — Of all the above-mentioned infectious diseases, Lyme borreliosis (Borrelia burgdorferi) is by far the most frequent infectious disease with a chronic course. In addition, this disease (Lyme borreliosis, Lyme disease) is the most thoroughly investigated of all the above-mentioned infectious diseases. On the basis of the special status of Lyme borreliosis, the other infections have been termed “coinfections” in the literature. Lyme borreliosis can be accompanied by one or more coinfections (double or multiple infections). Coinfections exacerbate the expression of the disease and hinder the therapeutic success. The symptomatology of Lyme borreliosis and the so-called coinfections exhibit high degrees of overlap. A subtle diagnostic analysis is required to account for all of the infectious diseases which could (possibly) be present. The diagnostic and therapeutic options in cases of chronic infectious diseases are limited. This applies to Lyme borreliosis and even more for the coinfections. No adequate laboratory methods are available for the important coinfection Bartonella henselae, and there are no official guidelines available with regard to its antibiotic treatment. All of the above-mentioned pathogens are capable of intracellular localization; thus, (with the exception of B. burgdorferi) only intracellularly acting antibiotics are used. Despite this, the failure rate of the antibiotic treatment of the coinfections is high; on the other hand, with particular regard to Bartonella henselae the opinions on an adequate antibiotic therapy are very controversial. Since the clinical and scientific significance of these chronic infectious diseases has meanwhile been recognized, it is now imperative to develop and improve diagnostic and particularly therapeutic measures for the chronic infectious diseases.

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