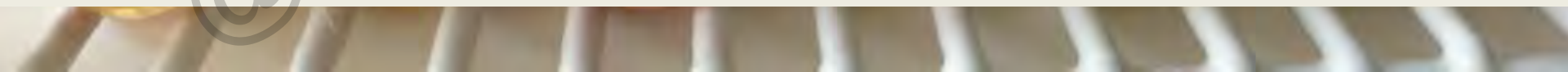
Laboratory support in the diagnosis of Lyme borreliosis
ECCMID2015 EW: 2015-0303

Borrelia Serology

from the perspective of the microbiologist

Gerold Stanek
Medical University of Vienna, Institute for Hygiene and Applied Immunology,
Center for Pathophysiology, Infectiology and Immunology
1090 Wien, Kinderspitalgasse 15



Exciting Discoveries

- Discovery of a new clinical entity: **Lyme arthritis** mid 1970s
- Detection of **spirochetes in hard t**icks in the early 1980s
- **Cultivation of these spriochetes** in artificial medium early 1980s

Steere AC, Hardin JA, Malawista SE. Lyme arthritis: a new clinical entity. Hosp Pract 1978; 13:143-58. Burgdorfer W, Barbour AG, Hayes SF, Benach JL, Grunwaldt E, Davis JP. Lyme disease – a tick-borne spirochetosis? Science 1982 ;216:1317-9.
Barbour AG. Isolation and cultivation of Lyme disease spirochetes. Yale J Biol Med 1984;57:521-5.
Steere AC, Grodzicki RL, Kornblatt AN, Craft JE, Barbour AG, Burgdorfer W, Schmid GP, Johnson E, Malawista SE. The spirochetal etiology of Lyme disease. N Engl J Med 1983;308:733-40.

Nosological entity

The newly discovered spirochete forms the nosological entity for many until then idiopathic disease manifestations of skin and nervous system, known for long in Europe; e.g.

- Erythema chronicum migrans
- Lymphadenosis benigna cutis/borrelial lymphocytoma
- Acrodermatitis chronica atrophicans
- Meningopolyneuritis (Garin-Bujadoux-Bannwarth)

Buchwald 1883 , Herxheimer & Hartmann 1902, Afzelius 1909, Lipschütz 1913, Garin & Bujadoux 1922, Bäfverstedt 1943, Bannwarth 1941, Hörstrup & Ackermann 1973

Borrelia burgdorferi sensu lato

Lyme disease spirochete

→ a new species of the genus *Borrelia.*

Antigenic variability between isolates from Europe and North America

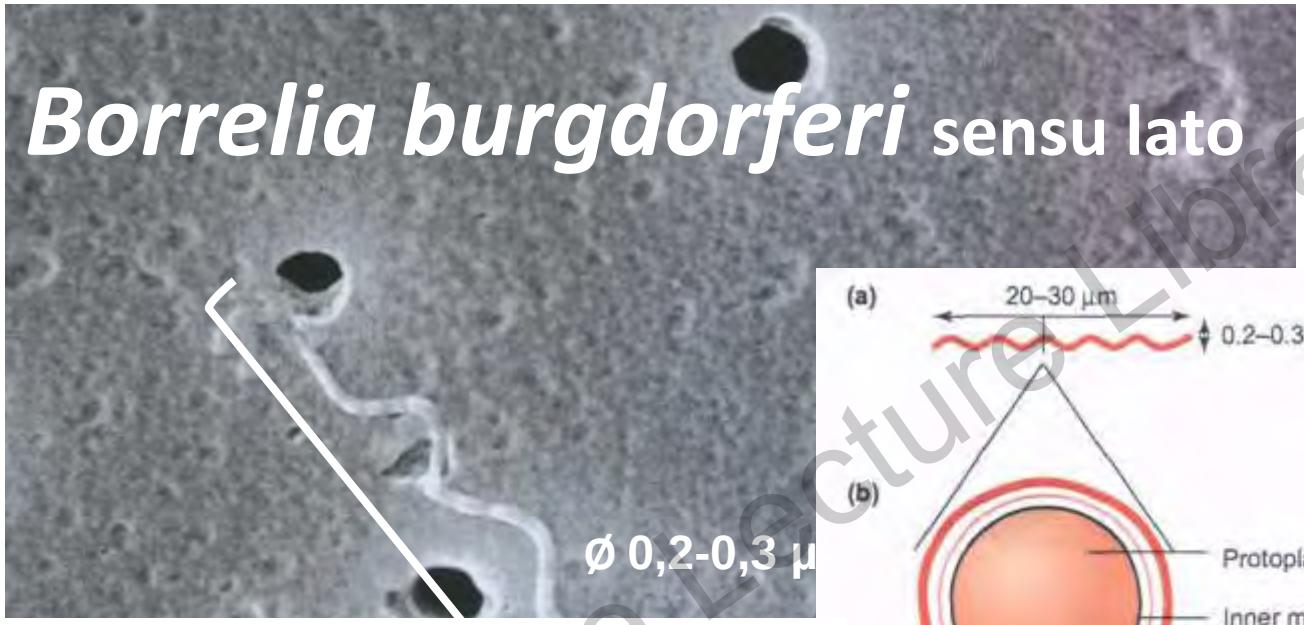
→ **OspA serotypes**

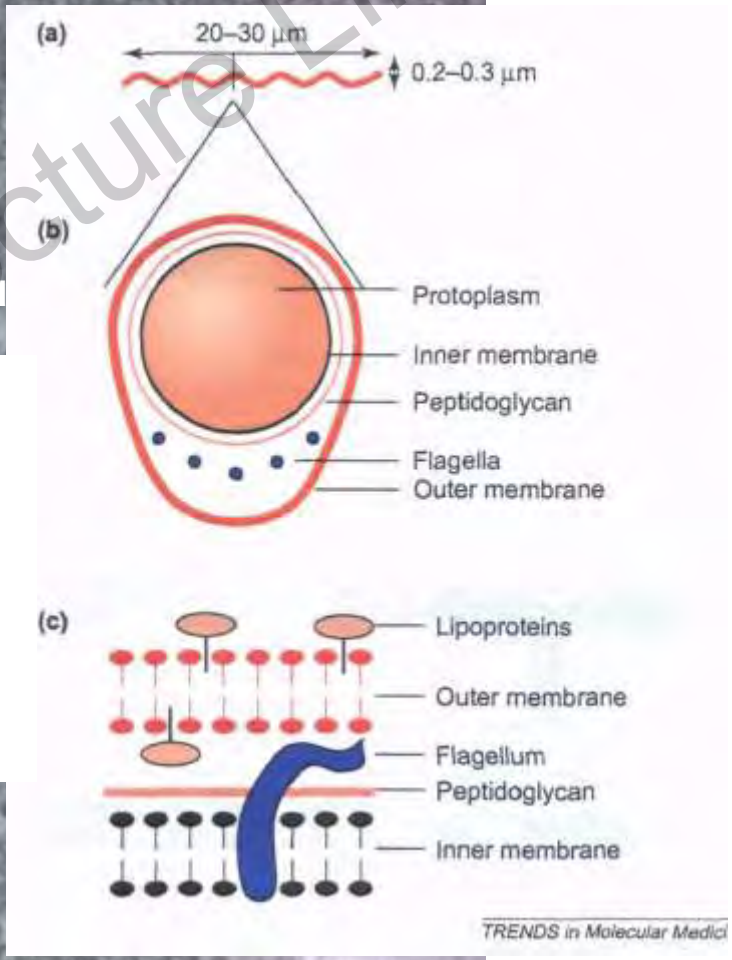
→ **Genospecies**: *Borrelia garinii*, *B. afzelii,* ….

today ca 20 genospecies

Johnson RC,. Schmid GP, Hyde FW, Steigerwalt AG, Brenner DJ. Borrelia burgdorferi sp. nov.: etiologic agent of Lyme disease. Int J Syst Bacteriol 1984; 34:496-497. Wilske B, Preac-Mursic V, Schierz G, Kühbeck R, Barbour AG, Kramer M. Antigenic variability of Borrelia burgdorferi. Ann N Y Acad Sci. 1988;539:126-43. Wilske B, Barbour AG, Bergström S, Burman N, Restrepo BI, Rosa PA, Schwan T, Soutschek E, Wallich R. Antigenic variation and strain heterogeneity in Borrelia spp. Res Microbiol. 1992;143:583-96. Baranton G, Postic D, Saint Girons I et al. Delineation of Borrelia burgdorferi sensu stricto, Borrelia garinii sp. nov., and group VS461 associated with Lyme borreliosis. Int J Syst Bacteriol 1992; 42: 378–383.

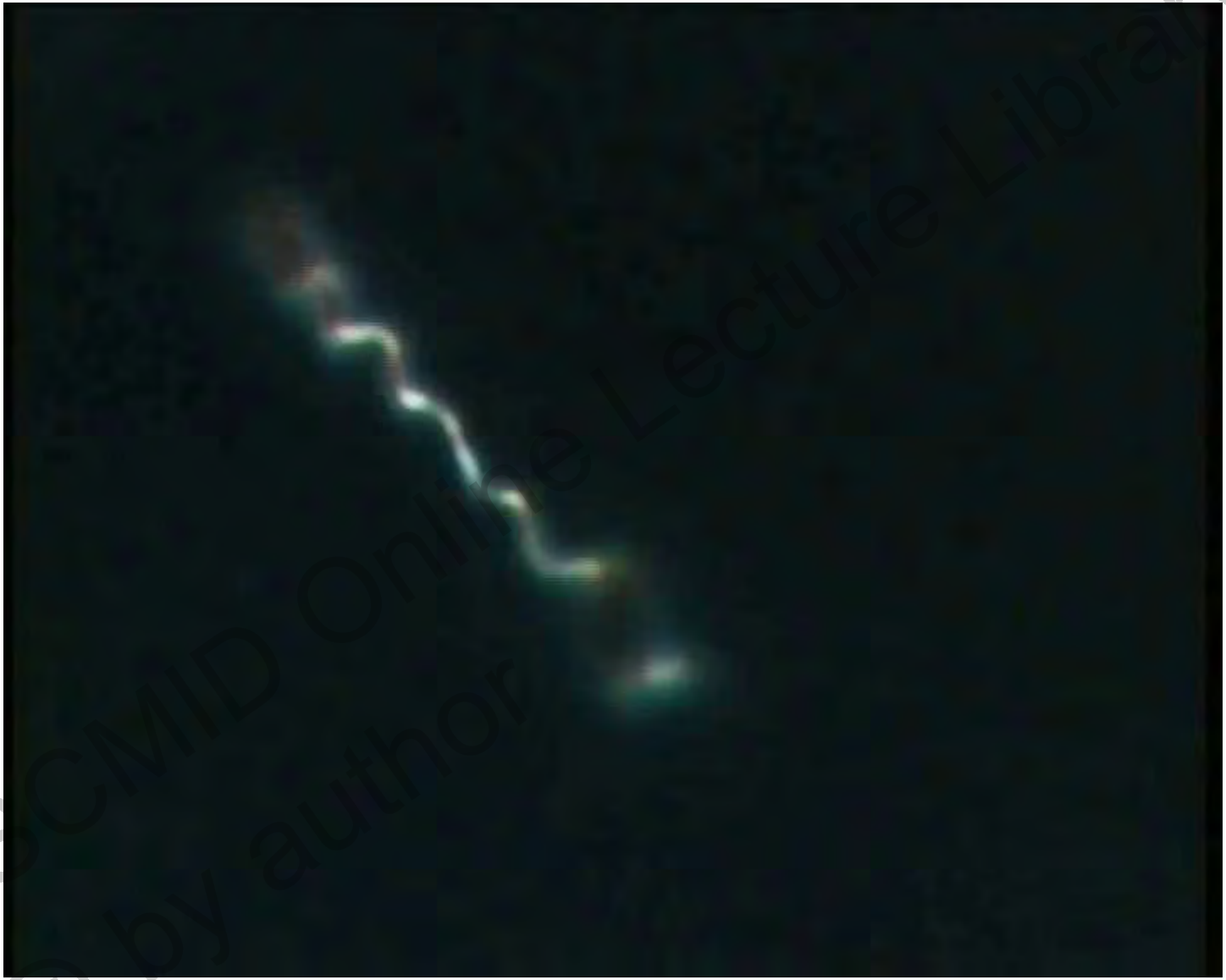
Borrelia burgdorferi sensu lato

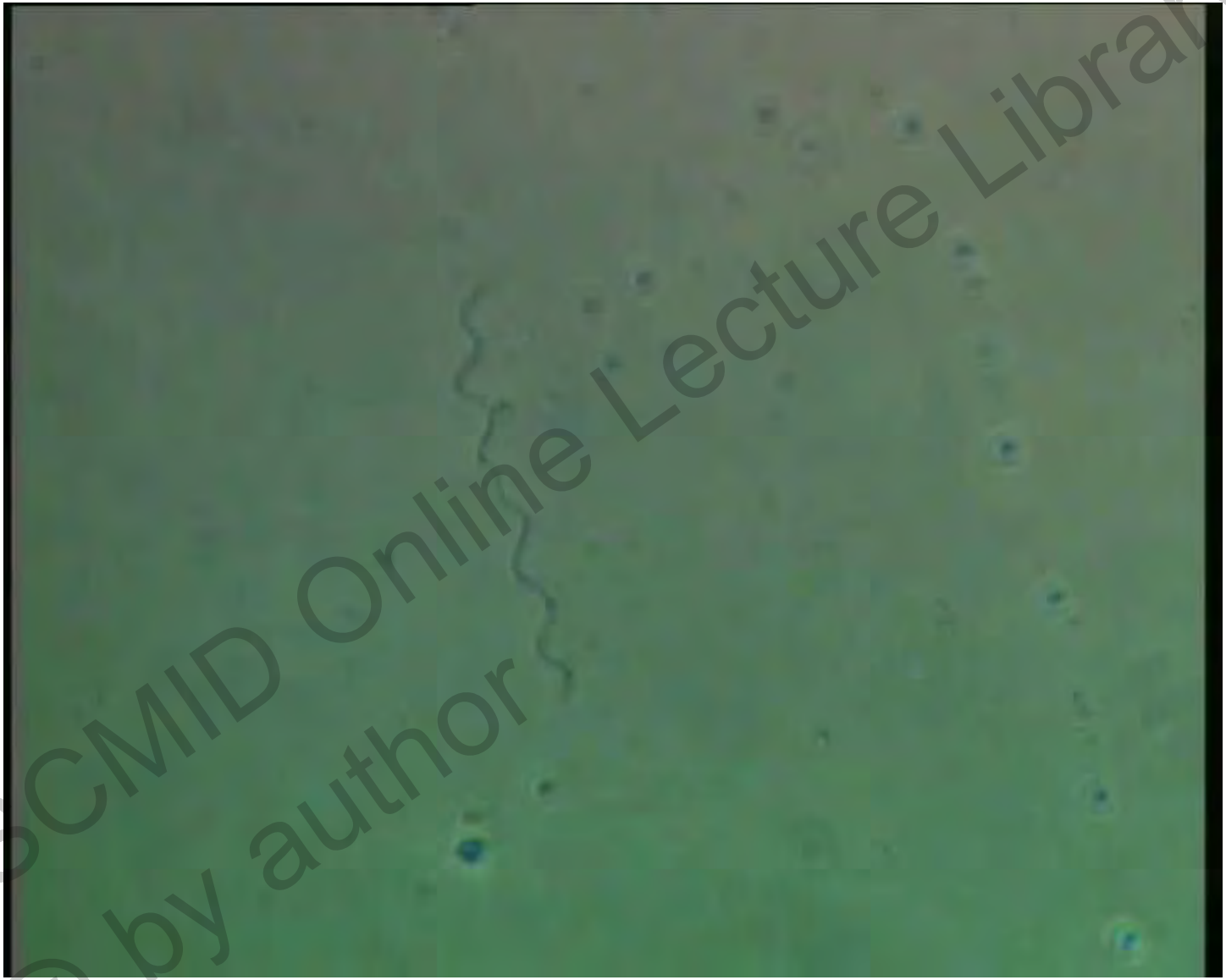




Pathogens of the *B. burgdorferi* sl-complex
Europe: *B. afzelii, B. garinii, B. bavariensis, B. burgdorferi* sensu stricto, (occ. *B. spielmanii*, *B. bissetii*, *B. valaisiana*, *B. lusitaniae)*
Asia: predominantly *B. garinii*
Northe America: exclusively *B. burgdorferi ss*

gerold.stanek@meduniwien.ac.at

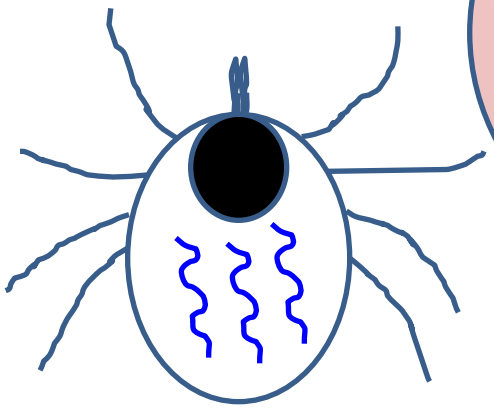





Infectious Cycle

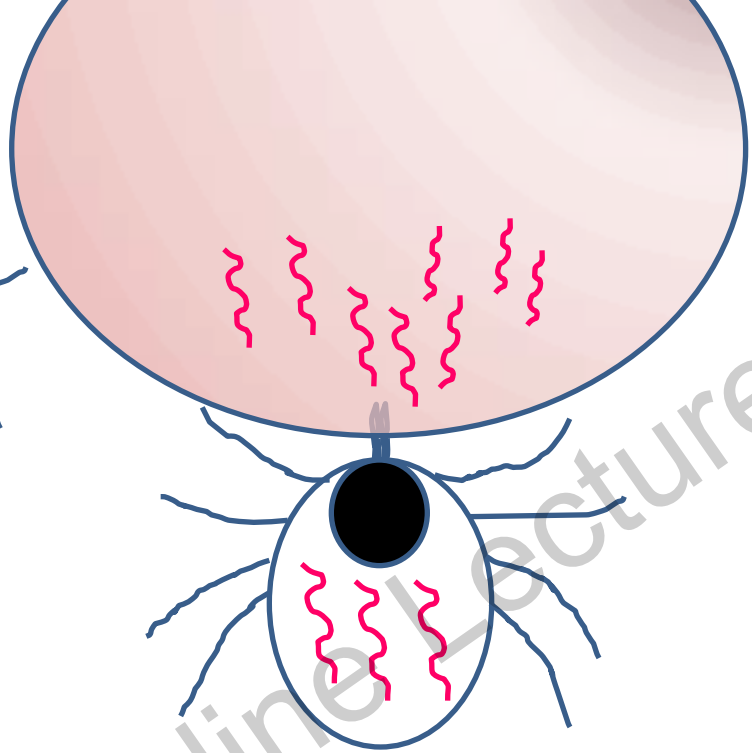
B. burgdorferi sl infectious cycle

- *B. burgdorferi sl* obligate tick-borne parasites
- **Reservoirs:** variety of **small mammals & birds**
- *B. burgdorferi* sl vectored by ticks of the genus *Ixodes*
- Ticks take up borreliae from infected reservoir animals during their **larval feeding**
- Ixodid ticks are the only natural vectors by which **humans** become infected with *B. burgdorferi* sl



unfed tick

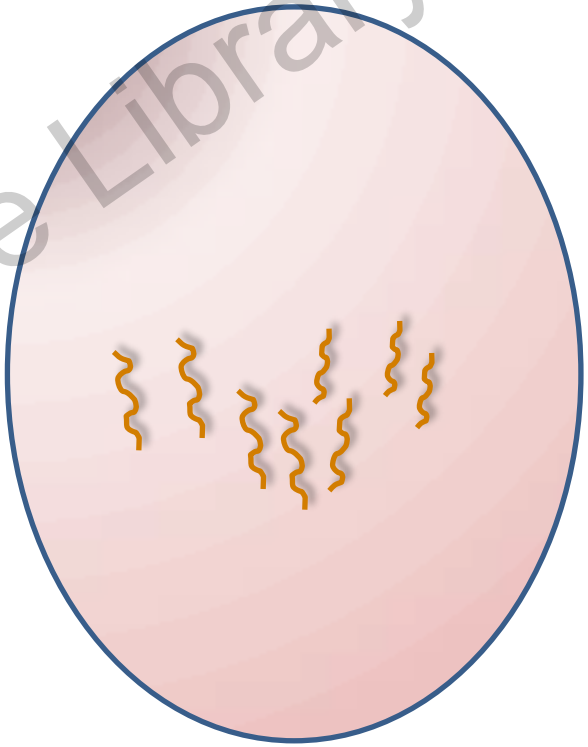
OspA on the outer membrane



Blood feeding tick

Onset of infection

OspC on the outer membrane



Infection

VlsE on the outer surface

Borrelia Serology

principle: two-tier testing

First tier
IgG & IgM
ELISA, IFAT, CLIA *etc.*

Lyme neuroborreliosis
CSF & serum
of the same day
→ CSF/serum antibody index (AI)

positive
or intermediate

negative

→ no further testing
with this specimen
→ if continuous
clinical suspect
→ control

Second tier
IgG and/or IgM
immunoblot

positive
report positive result

negative

report negative result

Borrelia serology essential?

Term	Clinical case definition	Laboratory evidence: essential	Laboratory/clinical evidence: supporting
Erythema migrans	Expanding red or bluish-red patch (≥5 cm in diameter)[a], with or without central clearing. Advancing edge typically distinct, often intensely coloured, not markedly elevated.	None	Detection of *Borrelia burgdorferi* s.l. by culture and/or PCR from skin biopsy.
Borrelial lymphocytoma (rare)	Painless bluish-red nodule or plaque, usually on ear lobe, ear helix, nipple or scrotum; more frequent in children (especially on ear) than in adults.	Seroconversion or positive serology[b] Histology in unclear cases	Histology. Detection of *B. burgdorferi* s.l. by culture and/or PCR from skin biopsy. Recent or concomitant EM.
Acrodermatitis chronica atrophicans	Long-standing red or bluish-red lesions, usually on the extensor surfaces of extremities. Initial doughy swelling. Lesions eventually become atrophic. Possible skin induration and fibroid nodules over bony prominences.	High level of specific serum IgG antibodies	Histology. Detection of *B. burgdorferi* s.l. by culture and/or PCR from skin biopsy.
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[c]In early cases intrathecally produced specific antibodies may still be absent.

Stanek G, Fingerle V, Hunfeld KP, Jaulhac B, Kaiser R, Krause A, Kristoferitsch W, O'Connell S, Ornstein K, Strle F, Gray J. Lyme borreliosis: Clinical case definitions for diagnosis and management in Europe. Clin Microbiol Infect 2011; 17: 69–79

Erythema migrans

♀ **31 years**
Tick bite in the umbilicus

after 2 weeks

Borrelia burgdorferi	
Borrelia spp.-IgG-AK (EIA) (<10,8 negativ, >13,2 positiv)	<10,8 AU/ml
Borrelia spp.-IgM-AK (EIA) (<12,6 negativ, >15,4 positiv)	<12,6 AU/ml

after 5 weeks

Borrelia burgdorferi	
Borrelia spp.-IgG-AK (EIA) (<10,8 negativ, >13,2 positiv)	>200,0 AU/ml
Borrelia spp.-IgM-AK (EIA) (<12,6 negativ, >15,4 positiv)	>200,0 AU/ml
Borrelia burgdorferi	
Borrelia IgG-Antikörper (IB)	positiv
Borrelia IgM-Antikörper (IB)	positiv

Erythema migrans

05.11.2012

Borrelia burgdorferi	
Borrelia spp.-IgG-AK (EIA) (<10,8 negativ, >13,2 positiv)	29,6 AU/ml
Borrelia spp.-IgM-AK (EIA) (<12,6 negativ, >15,4 positiv)	<12,6 AU/ml
Borrelia burgdorferi	
Borrelia IgG-Antikörper (IB)	positiv

17.06.2013

Three weeks ago small red line on theright upper arm, no insect bite

Borrelia burgdorferi	
Borrelia spp.-IgG-AK (EIA) (<10,8 negativ, >13,2 positiv)	33,8 AU/ml
Borrelia spp.-IgM-AK (EIA) (<12,6 negativ, >15,4 positiv)	<12,6 AU/ml
Borrelia burgdorferi	
Borrelia IgG-Antikörper (IB)	positiv

Treatment 2 weeks

after 1 month

Borrelia burgdorferi	
Borrelia spp.-IgG-AK (EIA) (<10,8 negativ, >13,2 positiv)	121,7 AU/ml
Borrelia spp.-IgM-AK (EIA) (<12,6 negativ, >15,4 positiv)	<12,6 AU/ml
Borrelia burgdorferi	
Borrelia IgG-Antikörper (IB)	positiv

♂ **68 years**

Borrelia serology essential

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Acrodermatitis chronica atrophicans

♀ **70 Jahre**

Three years ago EM right upper leg, now pains on heel and legs, skin discolorated
In August in Hospital because of tachycardic atrial fibrillation
dilatated CMP; Coronarangiography: no indication of CHD

Treatment 4 weeks

Borrelia burgdorferi	
Borrelia spp.-IgG-AK (EIA) (<10,8 negativ, >13,2 positiv)	>200,0 AU/ml
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Borrelia burgdorferi	
Borrelia IgG-Antikörper (IB)	positiv

Acrodermatitis chronica atrophicans

After 6 months

Borrelia burgdorferi	
Borrelia spp.-IgG-AK (EIA) (<10,8 negativ, >13,2 positiv)	>200,0 AU/ml
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Borrelia burgdorferi	
Borrelia IgG-Antikörper (IB)	positiv

Borrelia serology essential

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Lyme neuroborreliosis

♂ **54 years**

June: **tick bite** left shoulder

July: erythema migrans left shoulder, shortly after onset pain in the back, no treatment

August: intense muscle aches entire thorax when moving and breathing, over 3 weeks, then waning

September: acute pains in shoulder and both axillas, on the back, along the spine, entire thorax /inside muscle ache, on the surface like sunburn/ independent of moving; migrating muscle ache to the legs

pain predominantly at night → self medication: Ibuprofen without effect,

patient´s own suspect; Herpes zoster without eruption

October: at the neurologist (EEG, carotis ultrasound, questionnaire susp burn out), no Herpes zoster; suggested lumbar puncture refused because of gradual improvement.

Anew intense pain, excrutiating, sleepless; pat accepts **lumbar puncture**

October

Borrelia burgdorferi	
Borrelia spp.-IgG-AK (EIA) (<10,8 negativ, >13,2 positiv)	>200,0 AU/ml
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Borrelia burgdorferi	
Borrelia IgG-Antikörper (IB)	positiv

Intrathekaler Antikörpernachweis	
Serum IgG	>200,0 AU/ml
Liquor IgG	>200,00 AU/ml
Liquor/Serum-Index (<1,3 negativ, >1,5 positiv)	11,7

pleocytosis

Gesamt-Proteine Laser Nephelometer	
IgG im Serum (Referenzb. 800 - 1.700 mg/dl)	1.120 mg/dl
IgG im Liquor (Referenzb. < 4,0 mg/dl)	35,9 mg/dl
Albumin im Serum (Referenzb. 3.700 - 5.300 mg/dl)	4.830 mg/dl
Albumin im Liquor (Referenzb. < 35,0 mg/dl)	164,0 mg/dl

9 months after treatment

Borrelia burgdorferi	
Borrelia spp.-IgG-AK (EIA) (<10,8 negativ, >13,2 positiv)	109,4 AU/ml
Borrelia spp.-IgM-AK (EIA) (<12,6 negativ, >15,4 positiv)	<12,6 AU/ml

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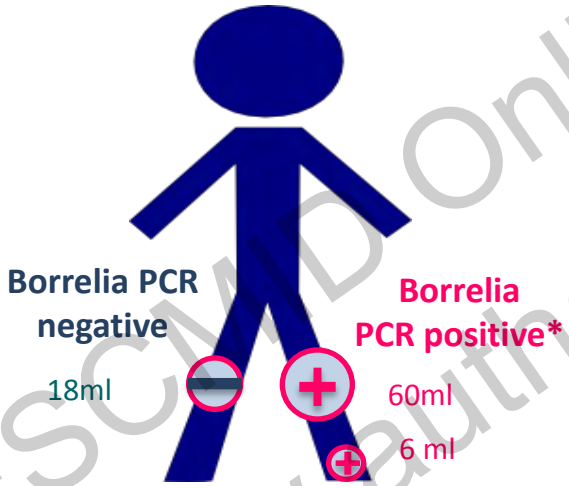
Course of Disease Lyme Arthritis

Age 11 yrs old boy since 5 yrs suffering from arthralgias
At yr 2: tick bite, no eErythema migrans
At yr 6: onset of recurring joint pain,
particularly left knee,
symptomatic treatment
At yr 10: swelling of the left knee for the first time
11 yrs old: Swelling of both knees and left ancle;
Puncture of all 3 joints

DIAGNOSTIC

Joints punctures, RT PCR with synovia



**** Borrelia bavariensis***

Laboratory results

Borrelia IgG-AK	**>200,0 AU/ml**	(>13.2)
Borrelia IgM-AK	<12.6 AU/ml	(>15.4)

Borrelia Immunoblot IgG positiv
VlsE, p83 ,p93, p30, p21, p19, p17

CRP 79.4 mg/L (>5mg/L)
RF, white blood cell cout, ANA, dsDNA
Mycoplasma pneumonie
Chlamydia spp.
Salmonella ABCD
Yersinia enterocolitica

*Real time PCR, targets: 16S rDNA and flagellin gene; genotype identification: nested PCR target: 5S–23S intergenic spacer → bidirectional sequencing; Osp A serotype identification: PCR, target: OspA gene, sequencing and RFLP → Osp A serotype [4]

Markowicz et al. Emerg Infect Dis in press

Tools for diagnosis

Borrelial Lymphocytoma *>90% Borrelia afzelii*	Previous or accompanying erythema migrans	**IgG- IgM-antibodies, seroconversion**	**Histology**		
Acrodermatitis chronica atrophicans ***89% Borrelia afzelii*** ***7% Borrelia garinii*** ***4% B burgdorferi ss***	**IgG antibodies**	**Histology**			
Lyme-neuroborreliosis ***63% Borrelia garinii*** ***23% Borrelia afzelii*** ***11% B. burgdorferi*** ***3% others***	**CSF-Cytology**	**↑ Total IgM oligoclonal bands**	**AI CSF/serum-Index >1,4**	**CXCL13 ?**	
Arthritis	Previous or accompanying erythema migrans	**direct detection by PCR**	**IgG antibodies**		
Carditis, ophthalmitis other …	Previous or accompanying EM	**direct detection by PCR,** culture	**Specific antibodies ?**		

Borrelia serology pros & cons

- ***confirm or reject*** *suspected clinical diagnosis*
- *interpret serological results with respect to* ***indication for treatment***
- ***confirm*** *success of treatment*

- ***IgG*** *in healthy persons*
- ***IgG*** *and* ***IgM*** *in persons with unspecific symptoms*
- *Isolated* ***IgM*** *in persons with unspecific symptoms*
- *Persons with unspecific symptoms: first tier* ***negative, second tier "confirmation test" positive***
- *Persons with unspecific symptoms, sero-negative but positive in cellular tests*
- *……*

Borrelia serology pros & cons

- **Borrelia serology without a relation** to suspect of **clinical** Lyme borreliosis →**predictive value very low**
- **Prevalence of IgG antibodies** to *B burgdorferi* sl in the average healthy population is **about 5%** … in tick-exposed groups eg hunters **up to 80%**

Munchhoff P, Wilske B, Preac-Mursic V, Schierz G. Antibodies against Borrelia burgdorferi in Bavarian forest workers. Zentralbl Bakteriol Mikrobiol Hyg A 1987;263:412-419. Cetin EM, Sotoudeh M, Auer H, Stanek G. Paradigm Burgenland: risk of Borrelia burgdorferi sensu lato infection indicated by variable seroprevalence rates in hunters. Wien Klin Wochenschr 2008;118: 677-681
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Thank you for your attention