Update: Therapie der chronischen Borreliose

Dr. med. Axel Hübner

Mitglied der Deutsche Borreliose-Gesellschaft

Mitglied der International Lyme and Associated Diseases Society (ILADS)

Ärztliche Fortbildung
AUGSBURG Februar 2016

Wechselwirkungen zwischen Erreger und Immunsystem des Betroffenen

Erreger:

Um welche(n) Erreger geht es?

Welche Virulenzfaktoren hat oder haben die Erreger (wie aggressiv ist er) ?

Patient (Betroffener, Infizierter, Wirt):

Welche Abwehrmechanismen sind vorhanden?

Ist das Immunsystem stark oder geschwächt?

Bakterielle Erreger (eine Auswahl, Beispiele)

Human-pathogene Borrelienstämme	**Ko-Infektionen**	**Sekundär- oder Begleitinfektionen**
Borrelia burgdorferi s.s.	Ehrlichia/Anaplasma spp.	Chlamydia spp.
Borrelia garinii	Bartonella spp.	Mykoplasma spp.
Borrelia afzelii	Babesia spp.	Yersinia enterocolica
Borrelia bavariensis	Rickettsia spp.	Toxoplasma gondii
Borrelia miyamotoi		
Borrelia spielmanii	Coxiella burnetii	

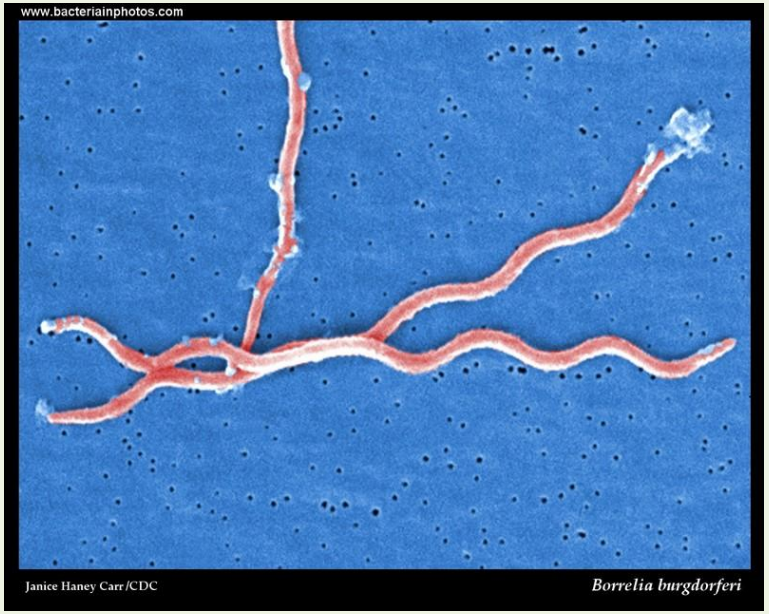
Virale Erreger (eine Auswahl, Beispiele)

Ko-Infektionen	**Sekundär- oder Begleitinfektionen**
FSME (TBE) – virus	EBV
Colorado- fever	CMV
Krim-Kongo-fever	Coxsackie
Kyasanur Forest Disease	Herpes spp
	Borna virus

Verschiedene Borrelienstämme und mehr..?

Anders gesagt: Wir müssen wahrscheinlich **komplexer** denken!

Es gibt **mehrere, human-pathogene** Borrelienstämme, die auch **gleichzeitig** im Patienten vorkommen können!
Das gilt auch für alle **anderen** Zecken-übertragenen Erreger und **Sekundär- oder Begleitinfektionen**!



Borrelien

Verschiedene Zustandsformen von Borrelien:

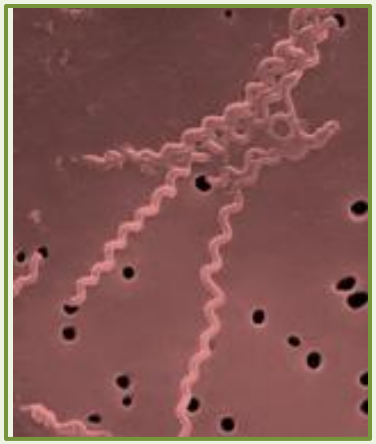
- Native Spiralform
- Pleomorphe Formen (Round bodies, Blebs, Loops, coccoid, etc.)
- Intrazelluläre Formen (auch wichtig bei anderen Erregern)
- Biofilme (auch wichtig bei anderen Erregern)

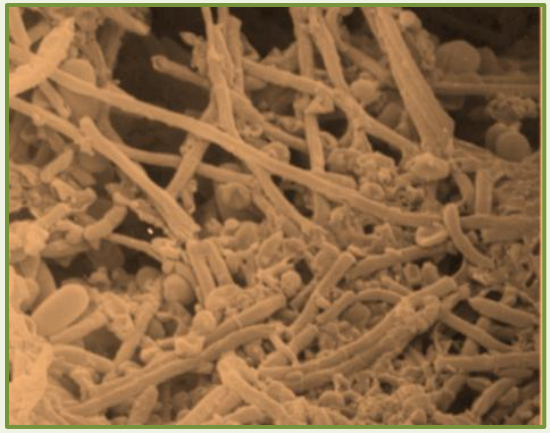
Physical forms of Borrelia

granular or coccoid form

round bodies

Physical Forms of Borrelia



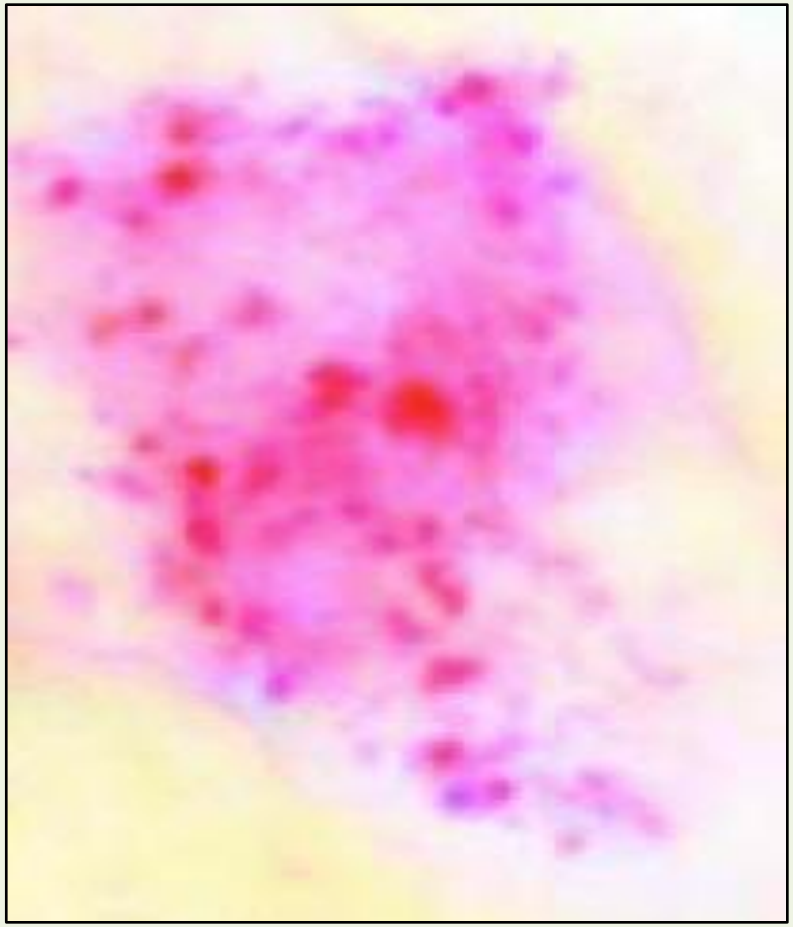


Spiral form

Biofilm

Pleomorphic forms of Borrelia allow evasion of the immune system and trigger chronic conditions.

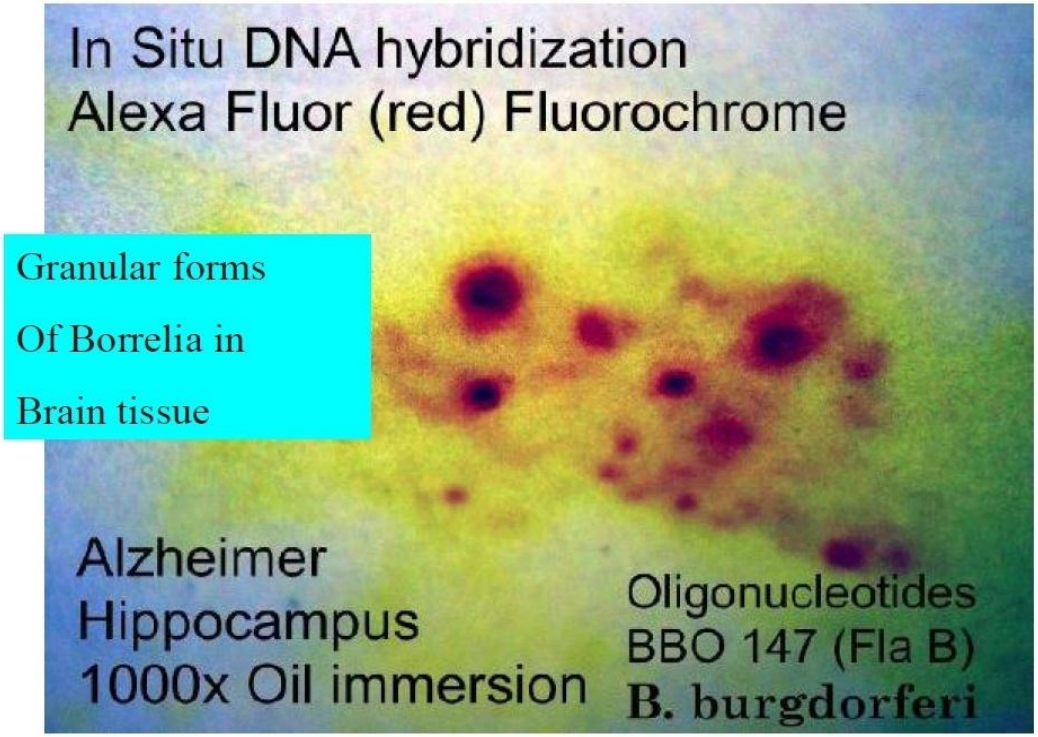
Borrelia: granular forms in vivo



Eisendle K. et al:
Acrodermatitis Chronica Atrophicans
Immunohistochemistry AJCP 2007,127:213-222

"Granular forms of *B burgdorferi* in a "colony" with a "Reddish veil"

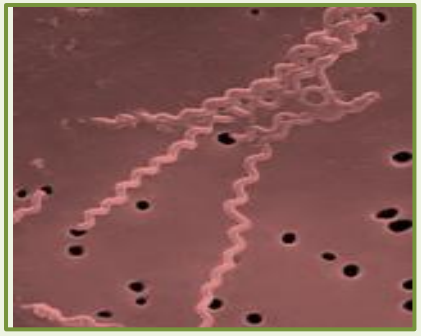
Borrelia: granular forms in Brain tissue in vivo



Mac Donald A: Concurrent Neocortical Borreliosis and Alzheimer's Disease Demonstration of a Spirochetal Cyst Form, *1988*

"An unexpected observation was the identification of cystic forms of the Borrelia spirochete in dark-field preparations of cultured hippocampus"

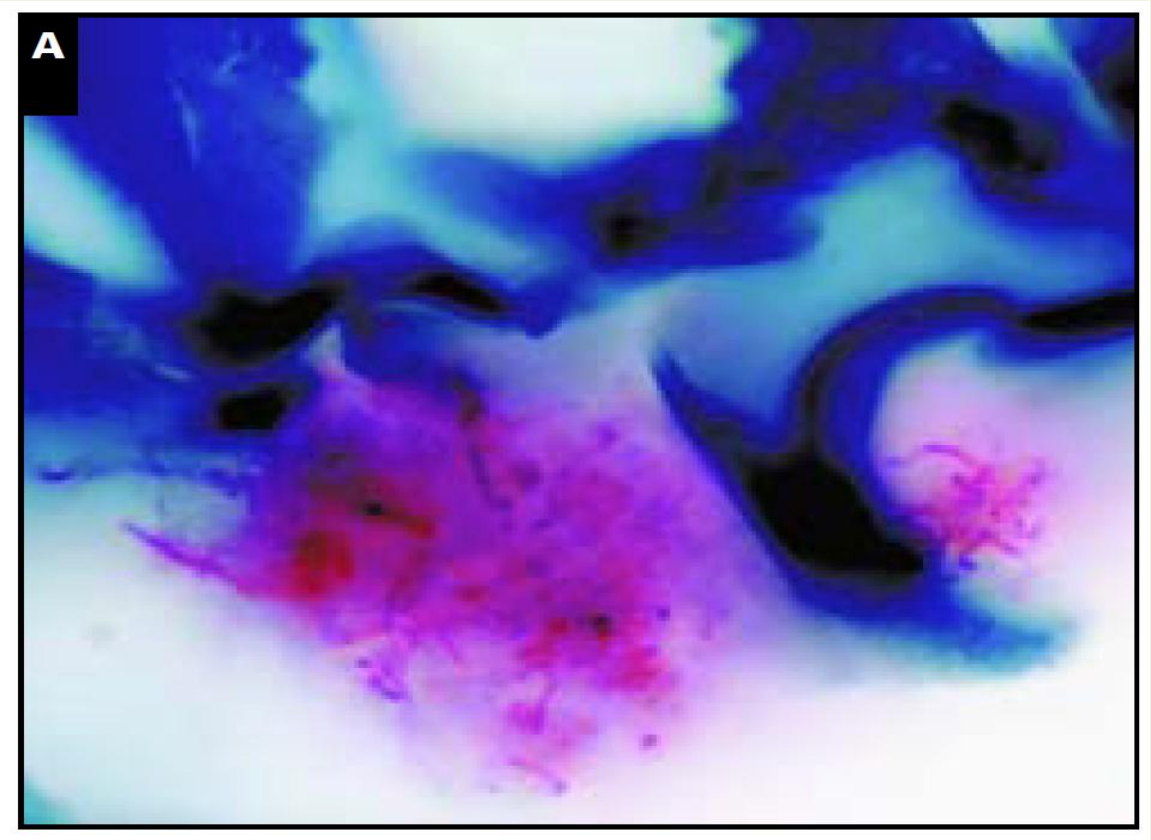
Borrelia: Conversion between the forms



Grunter et al: Conversion of Borrelia garinii Cystic Forms to Motile Spirochetes *In Vivo*. *Grunter, 2001*

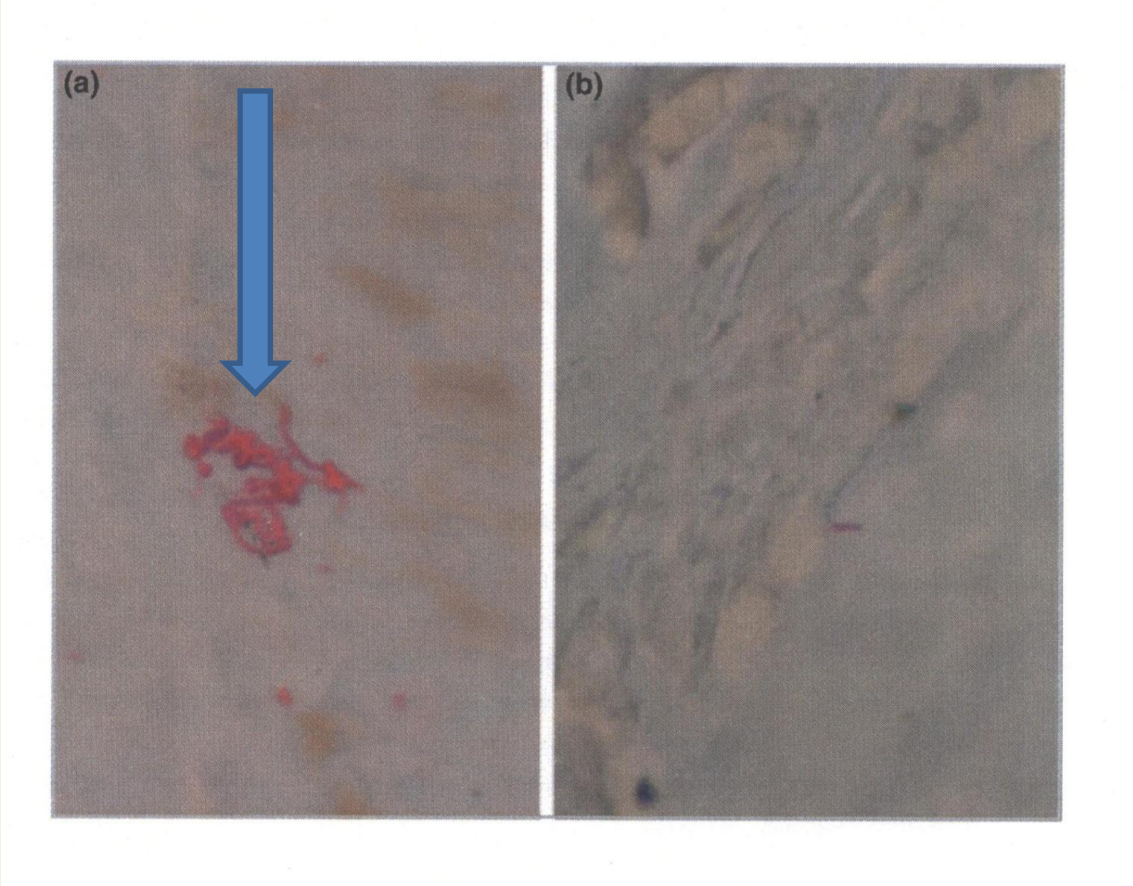
B. garinii cystic forms maintain their capability to reconvert into normal spirochetes not only in vitro but also in vivo and can therefore be considered infective, at least in BALB/c mice." "Dormant borreliae evacuated in cysts might be resistant to antibiotics (due to low metabolic activity) and stage under non-optimal environmental conditions. **Borrelial cystic forms could therefore be responsible for the frequent failures of antibiotic therapy and for the commonly reported relapses of Lyme disease.**

Borrelia: Biofilms in vivo



Eisendle A et al: 2007: *Borrelial lymphocytoma with medusa-like colony of Borrelia*.

Borrelia: Biofilms in vivo

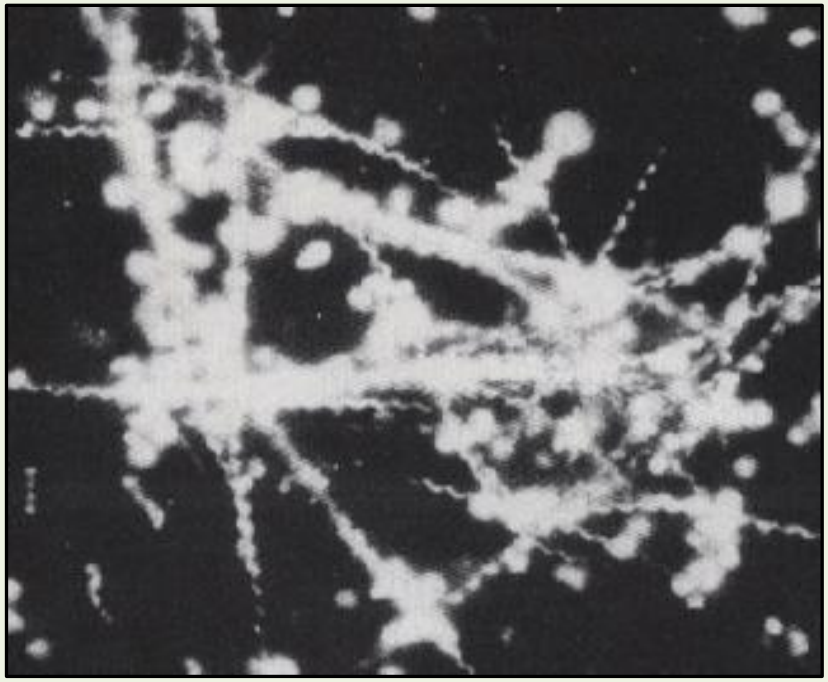


Eisendle et al, "Morphea" a manifestation of infection with Borrelia species, British J Dermatology 2007

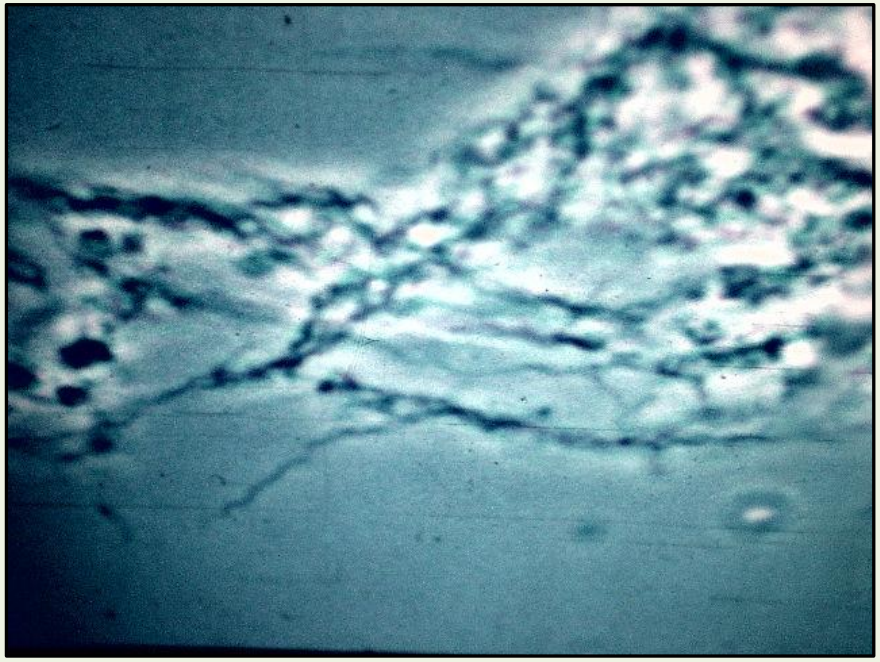
Morphea – with biofilm-like "clump" of Borrelia

UNIVERSITY OF NEW HAVEN

Borrelia: Biofilms in vivo

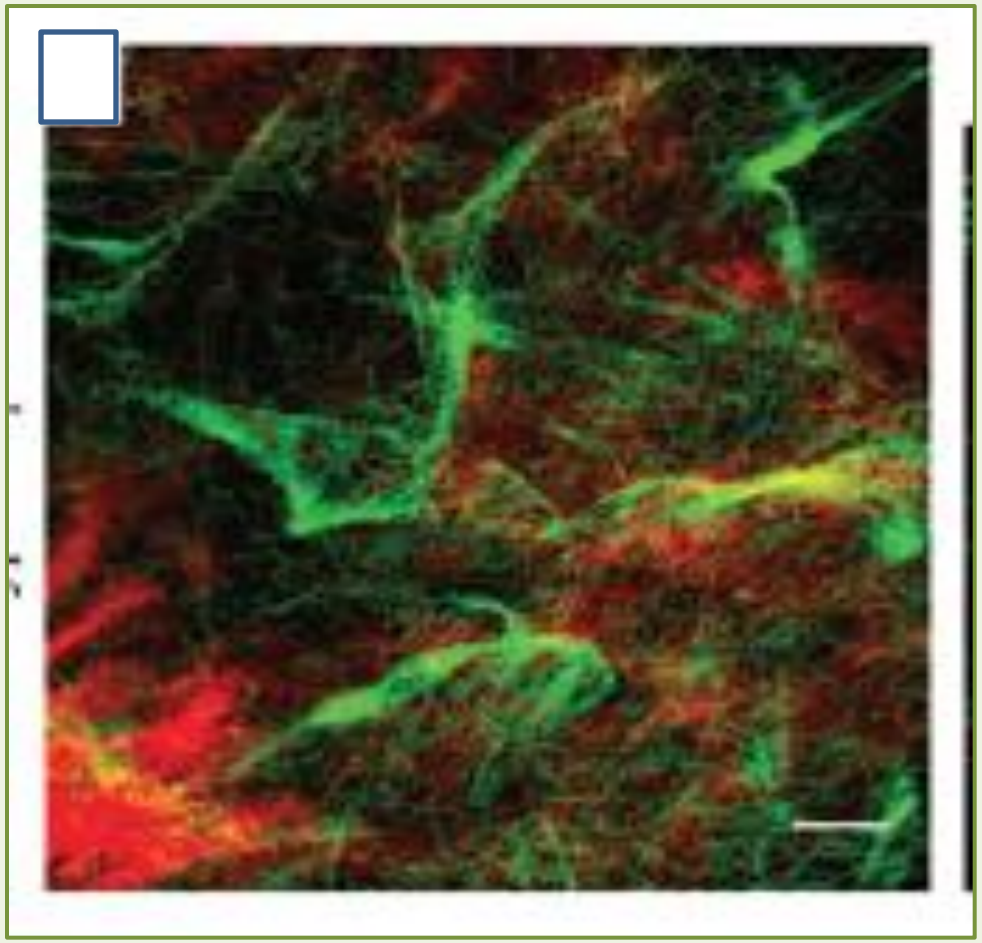


Human brain culture demonstrating a potential biofilm of *Borrelia burgdorferi,* 1987



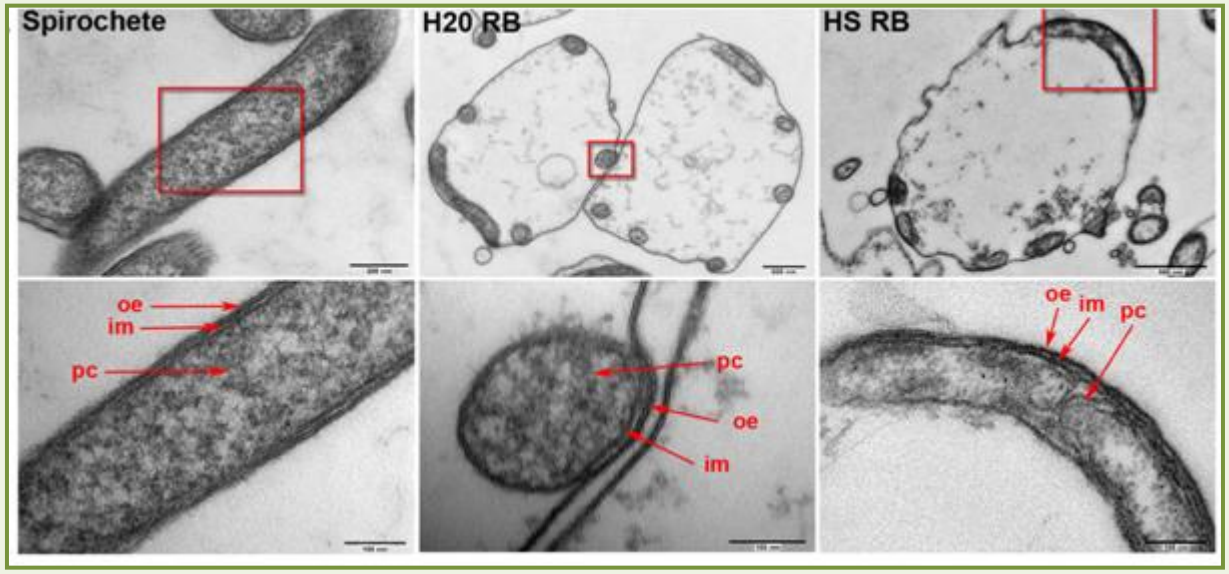
Tick gut culture showing *Borrelia burgdorferi* in a potential biofilm Unit; 1981

Borrelia: networks in vivo



Dunham-Ems et al 2009:
B. burgdorferi in nymphal midgut during feeding in the form of epithelial cell–associated networks

Borrelia: Atypical Cell Wall



Pleomorphic forms of *B. burgdorferi* are not cell wall deficient.
Transmission electron micrographs of epon embedded pleomorphic forms. Upper panel represents whole cell and expanded insets on the lower panel indicate the zoomed morphology of the outer membrane. The outer envelope (oe), inner membrane (im) and protoplasmic cylinder (pc) are easily discernible in zoomed images. Scale bar 5 µm.

Study: Meriläinen, L et al.: Morphological and biochemical features of Borrelia burgdorferi pleomorphic forms. Microbiology Papers in Press. Published January 6, 2015 as doi:10.1099/mic.0.000027.

Mechanismen für Erregerpersistenz

Borrelien entwickeln zahlreiche **Überlebens-mechanismen** in den verschiedensten Wirten, so z.B.:

a) Einnisten in schlecht durchblutete Gewebebereiche (Gelenke, Sehnen, Bindegewebe, Nervensystem)
b) Veränderung des makroskopischen Aussehens (pleomorphe Formen)
c) Veränderung der immunologischen Oberflächen
d) Bildung von Biofilmen

Borrelien: Veränderungen der immunologischen Oberfläche

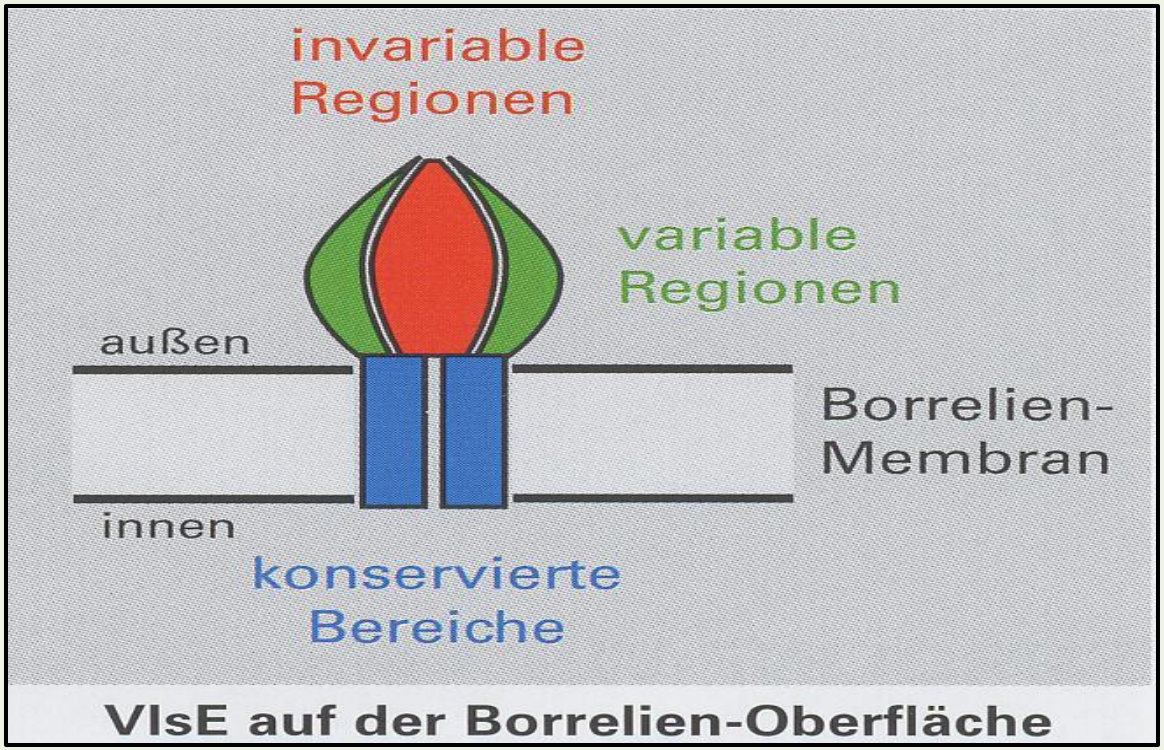
- Wechsel der Antigenität (wie HIV) z.B. mit den variablen Regionen des VlsE

- Beschichtung der eigenen Oberflächen mit FHL-1/Reconectin und damit Erreichen einer Resistenz gegen das Komplementsystem (bzw. Inaktivierung)

- Exprimieren von Antigenen, die zu einer Anbindung bestimmter Antikörper oder Gewebsmoleküle (Decorin, Fibronectin u.a.) des Wirtes führen und damit Aufbau einer „Schutzschicht“ gegen die Immunabwehr und Antibiotika

Borrelia: Variable Surface Marker VlsE

VlsE = Vmp-like sequence Expression site:
highly specific, associated to activity and variable



VlsE auf der Borrelien-Oberfläche

Borrelien: weitere Überlebensmechanismen

- Fähigkeit der Borrelien zur raschen Auf- und Abregulation von verschiedenen Genen: dadurch gelingt die Modulation der Immunsysteme von sehr verschiedenen Wirten (Säugetiere, Vögel, Zecken, Menschen) und somit das Überleben unter verschiedensten Bedingungen der unterschiedlichen Wirte (z.B. Temperatur, pH-Werte, Immunsysteme)

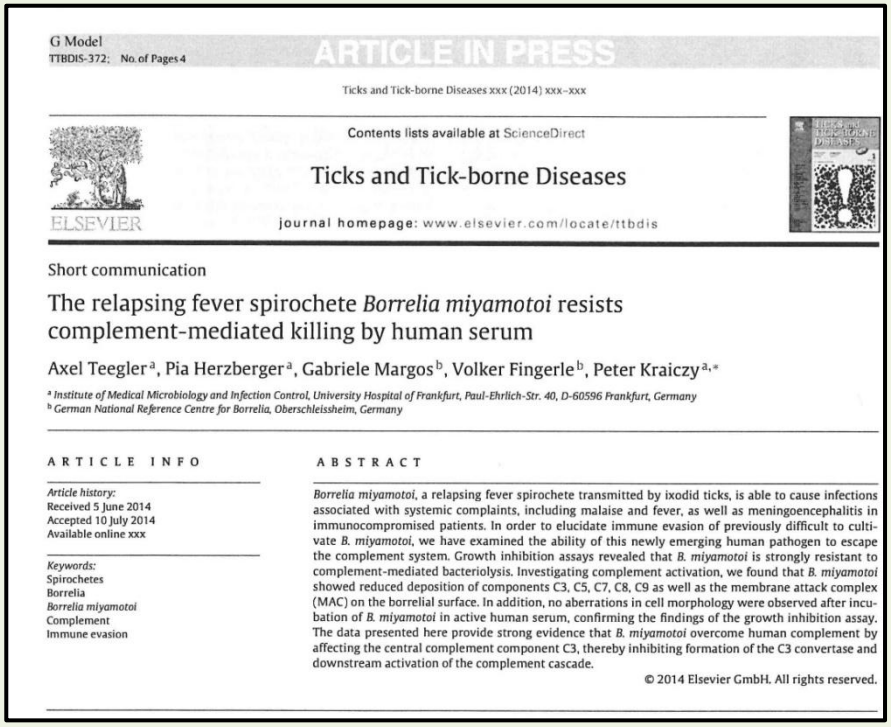
- Schutz durch „*Salp 15 Protein*“ im Zeckenspeichel

- Die Komplementresistenz (wichtiger Virulenzfaktor) der Borrelien ist abhängig vom jeweiligen Borrelienstamm und vom Komplementsystem des betroffenen Wirtes: wichtige Wechselwirkung

Hypothese: Die partielle, funktionelle Schwächung des Immunsystems führt zur Erkrankung!

- Die Resistenz von Borrelienstämmen gegenüber dem humanen Komplementsystem (einem wichtigen Teil unseres angeborenen Immunsystems) führt zu einer partiellen und funktionellen Immunschwäche (Ineffektivität des Abwehrsystems) und damit zur Erkrankung in Form von Symptomen.
- Welche Rolle oder Auswirkungen dies auch bei der Abwehr von anderen Erregern (Chlamydien spp., Mycoplasma spp., etc.) spielt bzw. hat , ist dabei sicher auch noch interessant, aber noch nicht untersucht worden.
- Diese Komplement-Resistenz und die daraus resultierende Ineffektivität der Immunabwehr (Schwäche) ist leider bisher mit keinem Routinelabortest messbar. Die Komplement-Resistenz existiert aber und ist bereits nachgewiesen für mehrere Borrelien spp.(siehe nachfolgende Folie und auch N. Satz: Klinik der Lyme-Borreliose, S. 173 ff)

Resistenz der Borrelien gegen das humane Complementsystem



G Model
TTBDIS-372; No. of Pages 4
ARTICLE IN PRESS
Ticks and Tick-borne Diseases xxx (2014) xxx–xxx
Contents lists available at ScienceDirect
Ticks and Tick-borne Diseases
journal homepage: www.elsevier.com/locate/ttbdis

Short communication

The relapsing fever spirochete *Borrelia miyamotoi* resists complement-mediated killing by human serum

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ABSTRACT

Borrelia miyamotoi, a relapsing fever spirochete transmitted by ixodid ticks, is able to cause infections associated with systemic complaints, including malaise and fever, as well as meningoencephalitis in immunocompromised patients. In order to elucidate immune evasion of previously difficult to cultivate *B. miyamotoi*, we have examined the ability of this newly emerging human pathogen to escape the complement system. Growth inhibition assays revealed that *B. miyamotoi* is strongly resistant to complement-mediated bacteriolysis. Investigating complement activation, we found that *B. miyamotoi* showed reduced deposition of components C3, C5, C7, C8, C9 as well as the membrane attack complex (MAC) on the borrelial surface. In addition, no aberrations in cell morphology were observed after incubation of *B. miyamotoi* in active human serum, confirming the findings of the growth inhibition assay. The data presented here provide strong evidence that *B. miyamotoi* overcome human complement by affecting the central complement component C3, thereby inhibiting formation of the C3 convertase and downstream activation of the complement cascade.

The relapsing fever spirochete *Borrelia miyamotoi* is cultivable in a modified Kelly-Pettenkofer medium, and is resistant to human complement

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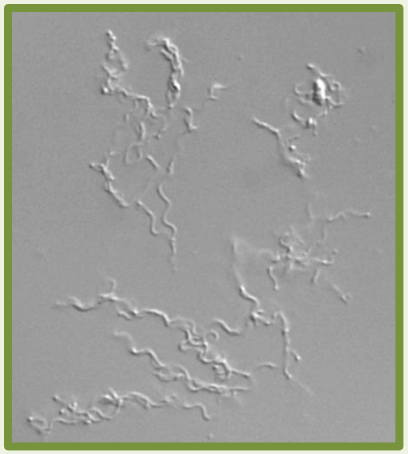
Abstract

Background

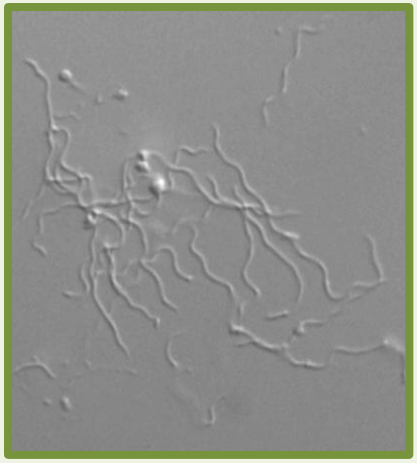
Borrelia miyamotoi is a relapsing fever spirochete found in *Ixodes* ticks in North America, Europe, and Asia, and has recently been found to be invasive in humans. Cultivation of this spirochete has not yet been described, but is important for patient diagnostics and scientific purposes. Host specificity of *Borrelia* species is dependent on resistance to host complement (serum resistance), and since *B. miyamotoi* has been identified as a human pathogen we were interested whether *B. miyamotoi* is resistant to human complement.

Borrelia, Co-Infections and Secondary Infections

Borrelia afzelii

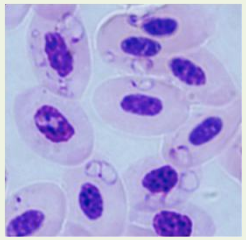


Borrelia garinii



Borrelia, Co-Infections and Secondary Infections

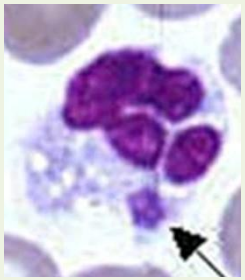
Babesia microti



http://www.healthinset.com/wp-content/uploads/2013/01/Babesia-Picture.jpg

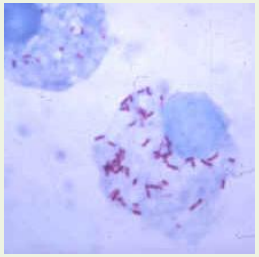
Bartonella henselae

Ehrlichia ewingii



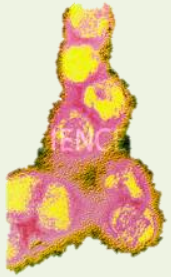
http://www.capcvet.org/capc-recommendations/7ehrlichia-spp-and-anaplasma-spp1/

Rickettsia rickettsii



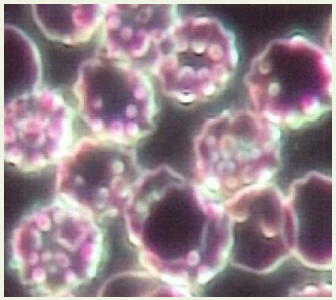
http://textbookofbacteriology.net/Rickettsia_2.html

TBE



Borrelia, Co-Infections and Secondary Infections

Chlamydia pneumoniae



http://www.cpnhelp.org/book/export/html/408

Mycoplasma fermentans

- EBV
- CMV
- HSV
- Coxsackie
- Borna

Studien: Ko-Infektionen 1

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

CURRENT CONCEPTS

Human Babesiosis

Edouard Vannier, Ph.D., and Peter J. Krause, M.D.

HUMAN BABESIOSIS IS AN INFEC
rocytic protozoa of the genus b
Babes, the Hungarian patholog
traerythrocytic microorganisms as the c
1888.[1] Five years later, Theobald Smith a
as the vector for transmission of *Babesia*
servation established for the first time t
tious agent to a vertebrate host.

The first documented human case of
a half century later, when a splenectomiz
to an infection subsequently attributed to
competent person was identified on Nan
setts, in 1969.[4] The causative agent wa

STATE-OF-THE-ART REVIEW ARTICLE

Beyond Cat Scratch Disease: Widening Spectrum of *Bartonella henselae* Infection

Todd A. Florin, MD[a,b], Theoklis E. Zaoutis, MD, MSCE[b,c,d,e], Lisa B. Zaoutis, MD[a,b]

Divisions of [a]General Pediatrics and [c]Infectious Diseases, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania; Departments of [b]Pediatrics and [d]Epidemiology and [e]Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania

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ABSTRACT

Bartonella henselae was discovered a quarter of a century ago as the causative agent of cat scratch disease, a clinical entity described in the literature for more than half a century. As diagnostic techniques improve, our knowledge of the spectrum of clinical disease resulting from infection with *Bartonella* is expanding. This review summarizes current knowledge regarding the microbiology, clinical manifestations, diagnostic techniques, and treatment of *B henselae* infection.

www.pediatrics.org/cgi/doi/10.1542/peds.2007-1897

doi:10.1542/peds.2007-1897

Key Words

Bartonella, cat scratch disease, lymphadenopathy, fever of unknown origin, hepatosplenic disease

Abbreviations

CSD—cat scratch disease
VEGF—vascular endothelial growth factor
FUO—fever of unknown origin

CAT SCRATCH DISEASE (CSD) has been reported in the literature for more than half a century as a syndrome of regional lymphadenopathy and fever. However, it has been only a quarter of a century since *Bartonella henselae* was identified as the etiologic agent. As diagnostic techniques have improved, *Bartonella* has been found to

Studien: Ko-Infektionen 2

Deutsches Ärzteblatt: Ehrlichien: Durch Zecken ub

aerzteblatt.de

MEDIZIN

Ehrlichien: Durch Zecken übertragbare Erreger

Dtsch Arztebl 2000; 97(38): A-2458 / B-2097 / C-1965

Bogdan, Christian; Baumgarten, Birgit Uta; Röllinghof, Martin

Zusammenfassung

Ehrlichien werden von Zecken auf den Menschen übertragen. Sie vermehren sich in Monozyten/Makrophagen oder Granulozyten und können zu schweren, akuten oder chronischen Krankheitszuständen mit Fieber, Schüttelfrost, Kopfschmerzen, Myalgien, Arthralgien, Leber- und Nierenfunktionsstörungen führen. Ehrlichiosen gehören zu den „neu aufgetretenen" Infektionskrankheiten („emerging infectious diseases"), die aufgrund der Nichtanzüchtbarkeit mit klassischen mikrobiologischen Verfahren bisher selten diagnostiziert wurden. In Süddeutschland sind etwa 1,6 bis 4 Prozent der Zecken mit granulozytären Ehrlichien infiziert. Bei Fieber unklarer Ursache mit Leukozytopenie, Thrombozytopenie oder Erhöhung der Transaminasen sollte während der Zeckensaison eine Ehrlichien-Diagnostik erfolgen.

Schlüsselwörter: Ehrlichien, Ehrlichiosis, humane granulozytäre Ehrlichiose (HGE), „emerging infectious diseases"

Summary

Tick-Transmitted Agents: Ehrlichia Species

Ehrlichia species are transmitted to humans by ticks. They multiply
monocytes/macrophages or granulocytes and may cause serious
diseases with fever, chills, headache, myalgia, arthralgia, and disc
function. Ehrlichiosis is considered an "emerging infectious diseas
because of the inability to culture these organisms by classical mi
procedures. In Southern Germany 1.6 to 4 per cent of ticks are inf
case of fever of unknown origin in combination with leukopenia, th
elevated liver enzyme levels during the tick season investigation f
recommended.

JNNP

Neuralgic amyotrophy associated with *Bartonella henselae* infection

Cari J Stek, Jeroen J J van Eijk, Bart C Jacobs, et al.

J Neurol Neurosurg Psychiatry published online August 14, 2010
doi: 10.1136/jnnp.2009.191940

Studien: Ko-Infektionen 3

Feature Article

Mycoplasmal Infections in Chronic Illnesses:

Fibromyalgia and Chronic Fatigue Syndromes, Gulf War Illness, HIV-AIDS and Rheumatoid Arthritis

Garth L. Nicolson, PhD, Marwan Y. Nasralla, PhD, Joerg Haier, MD, PhD, Robert Erwin, MD, Nancy L. Nicolson, PhD, Richard Ngwenya, MD

ABSTRACT Invasive bacterial infections are associated with several acute and chronic illnesses, including: aerodigestive diseases such as Asthma, Pneumonia, Inflammatory Bowel Diseases; rheumatoid diseases, such as Rheumatoid Arthritis (RA); immunosuppression diseases such as HIV-AIDS; genitourinary infections and chronic fatigue illnesses such as Chronic Fatigue Syndrome (CFS), Fibromyalgia Syndrome (FMS) and Gulf War Illnesses (GWI). It is now apparent that such infections could be (a) causative, (b) cofactors or (c) opportunistic agents in a variety of chronic illnesses. Using Forensic Polymerase Chain Reaction we have looked for the presence of one class of invasive infection (mycoplasmal infections) inside blood leukocyte samples from patients with CFS (Myalgic Encephalomyelitis), FMS, RA, and GWI. There was a significant difference between symptomatic CFS, FMS, GWI, and RA patients with positive mycoplasmal infections of any species (45-63%) and healthy positive controls (~9%) ($P<0.001$). This difference was even greater when specific species (*M. fermentans*, *M. hominis*, *M. penetrans*, *M. pneumoniae*) were detected. Except for GWI, most patients had multiple mycoplasmal infections (more than one species of mycoplasma). Patients with different diagnoses but overlapping signs and symptoms often have mycoplasmal infections, and such mycoplasma-positive patients generally respond to multiple cycles of particular antibiotics (doxycycline, minocycline, ciprofloxacin, azithromycin, and clarithromycin). Multiple cycles of these antibiotics plus nutritional support appear to be necessary for successful treatment. In addition, immune enhancement and other supplements appear to help these patients regain their health. Other chronic infections may also be involved to various degrees with or without mycoplasmal infections in causing patient morbidity in various chronic illnesses.

Warum: Ganzheitliche Therapie?

Diese komplexen und multifaktoriellen Ursachen aus den Vorbetrachtungen erfordern nach unserer Ansicht einen **individuellen** und **ganzheitlichen** Therapieansatz, der sich nach der speziellen Situation des Patienten richten sollte.

Welche Infektionen und welche Situation des individuellen Immunsystems liegen vor?

Dabei sollte man auch immer diese Möglichkeiten der Bildung von Persisterformen und Biofilmen durch die Erreger allgemein mit beachten (das gilt nicht nur für die Borrelien).

Ganzheitlicher Therapieansatz

Bei chronischen und/oder schwerwiegenden Krankheitsverläufen empfiehlt sich **neben** der Therapie mit **Antibiotika** auch eine **gezielte Begleittherapie** sowie **interdisziplinäre** Therapie:

1. **Antibiotika**
2. **Ernährungsumstellung** (Stärkung des Immunsystems, Hemmung von Entzündungsprozessen)
3. **Zielgerichtete Nahrungsergänzung** (Vitamine , Mineralstoffe, Essentielle Fettsäuren (Omega 3 u.a.), Probiotika, Co-Enzym Q10)
4. **Komplementärmedizinische Therapien** (Naturheilkunde) als Ergänzung der Antibiose oder auch alleinige Therapie möglich (z.B. wilde Karde, Artemisinin, Resveratrol, Knoblauch-Allicin, jap. Knöterich Kapuzinerkresse, Rosmariensäure, Brennessel, Monolaurinsäure, Hagebutte, Teufelskralle, Cranberry, etc.)
5. **Schmerztherapie** (WHO-Schema, physikalische Therapien)
6. **Physiotherapie und Bewegungstherapie**
7. **Psychotherapeutische Begleitung**

Antibiotikatherapie

- Zur Eliminierung oder Reduzierung der Borrelien und eventuell vorhandener Ko-Erreger
- Auswahl der Antibiotika unter Berücksichtigung der verschiedenen Zustandsformen der Borrelien (spirale Form, round bodies, Biofilme, intrazell. Formen)
- Auswahl der Antibiotika auch nach den begleitenden Ko-und Begleit-Infektions-Erregern und deren möglichen Zustandsformen (z.B. intrazellulär, Biofilme)
- Ausreichend lange Therapiedauer unter Berücksichtigung der langen Lebenszyklen von Borrelien (langsam wachsende Bakterien wie z.B. auch TBC-Bakterien).

Lyme-Borreliose: Therapieempfehlungen

<u>Stadium I (Orale Therapie)</u>

- Dauer: 4 – 6 Wochen
- oder bis zum Verschwinden der „Wanderröte“ bzw. des Lymphozytoms einnehmen

Doxycyclin (ab 8. Lebensjahr) **200- 400 mg/d für mind. 28 d**

Empfehlung: Doxycyclin-Spiegel im Serum bestimmen!

Cefuroxim* **2 x 0,5g/d für mind. 28 d**

Amoxicillin* **3 x 0,5g/d für mind. 28 d**

Azithromycin* **1. Woche: 1 x tgl. 1 Tbl. (500 od. 600mg) für 5 d**

2./3. Woche: 1 x tgl. 1 Tbl. (500 od. 600mg) Mo, Mi, Fr

*bei Kindern unter 8 Jahren und Schwangeren

- Unterstützung Gastrointestinaltrakt durch Probiotika/Symbiotika
- zusätzlich regelmäßige Laborkontrollen (Blutbild, Leber- und Nierenwerte)

Recommendations: Stade 1 (Early stage)

Medication	Dosage	Duration
Doxycycline (> 8 years old)	200- 400 mg a day (depending on doxy-level in blood!)	min. 28 days
Cefuroxim*	2 x 0,5 g a day	min. 28 days
Amoxicillin*	3 x 0,5 g to 1 g a day	min. 28 days
Azithromycine*	First week: 1 x tgl. 1 Tbl. (500 or 600mg) From 2nd week on: 1 x daily. 1 Tbl. (500 or 600mg)	for 5 days Mon, Wed, Fri

* For children under 8 years and pregnant patients

Antibiotika-Kombination für Spätformen

Cell Wall	Round bodies	Intracellular
Betalactams:	Plaquenil/Quensyl	**Macrolides:**
Amoxicillin	(Tinidazole)	Azithromycin
Penicillin G benzathine	(Metronidazole)	Clarithromycin
Cephalosporins:	Artemisin	Clindamycin
Ceftriaxon i.v.	Atovaquone	**Quinolones:**
Cefotaxim i.v.		Ciprofloxacin
Cefuroxim		Levofloxacin
Cefdinir		Moxifloxacin
Cefpodoxime		**Rifampicin**
		Tetracyclines:
		Doxycycline
		Minocycline

Studie: Antibiotika-Kombinationstherapien bei anderen Infektionen

New insights into *Chlamydia* and arthritis. Promise of a cure?

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Handling editor Tore K Kvien

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ABSTRACT

Chlamydia trachomatis and *Chlamydia pneumoniae* together comprise the most frequent causative pathogens that elicit reactive arthritis (ReA). Advances in our understanding of the molecular biology/molecular genetics of these organisms have improved significantly the ability to detect chlamydiae in the joint for diagnostic purposes, as well as extending our current understanding of the pathogenic processes they elicit in the joint and elsewhere. An important aspect of the latter is that synovial chlamydiae infect the joint in an unusual but metabolically active state. While some standard treatments can provide a palliative effect on the ReA disease phenotype, many reports have indicated that standard antibiotic treatment does not provide a cure. Of critical importance, however, two recent reports of controlled clinical trials demonstrated that *Chlamydia*-ReA can be treated successfully using combination antibiotic therapy. These observations offer the opportunity of a cure for this disease, thereby increasing the practical importance of awareness and diagnosis of the spondyloarthritis caused by *Chlamydia*. In this viewpoint, we provide an overview of recent key findings in the epidemiology, pathophysiology, clinical manifestations, diagnosis and treatment of *Chlamydia*-induced arthritis. Our intention is for these insights to be translated rapidly into clinical practice to overcome misdiagnosis and underdiagnosis of the disease, and for them to stimulate the continued development of a cure.

INTRODUCTION

That chlamydial infection acts as a trigger for Reiter's syndrome and reactive arthritis (ReA) has been known for many years. However, it has become clear during the last two decades that the two species primarily responsible for causing arthritis, *Chlamydia trachomatis* and *Chlamydia pneumoniae* elicit arthritis by their persistence in the joint.[1 2] Interestingly, evidence now exists indicating a chlamydial aetiology for at least some patients

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joint. Regardless, in this review we mainta
designation CReA in accordance with the
classification as part of ReA and SpA (howe
refs 28, 29).

EPIDEMIOLOGY

Genital infections with *C trachomatis* are
the most common sexually transmitted inf

Antichlamydial therapy of the arthritis

Identification of *Chlamydia* and/or other bacteria in joints initiated several studies to test various antibiotics for their elimination of pathogens from that site; all trials using antibiotic monotherapy were unsuccessful (cf refs 97, 98). However, a recent trial demonstrated positive results using an antibiotic combination in chronic SpA, with a special focus on *Chlamydia*.[99] This was followed by a study in patients with demonstrated CReA which showed that a 6-month course of combination therapy with rifampicin (300 mg/day) plus doxycycline (200 mg/day), or plus azithromycin (500 mg/day followed by 5 days of 2–500 mg once/week) is effective in eliminating pathogens, giving improvement of arthritis; patients in this study were shown to be PCR-positive either in blood or joint fluid for *C trachomatis* or *C pneumoniae*.[5 6] A response was observed in 63% versus 22%, and complete remission was observed in 20% versus 0% under active treatment compared with placebo, respectively. The combination of azithromycin and rifampin was most effective, although the study was not powered to determine which combination of antibiotics is superior. These results open for the first time the prospect for curative treatment. However, the effectiveness of this approach must be confirmed in additional studies, especially in patients diagnosed only by serology and clinical manifestations for chlamydial infection.[7]

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Häufig haben Patienten mit Borreliose auch Infektionen mit Chlamydia spp.

OPEN

Emerging Microbes and Infections (2014) 3, e49; doi:10.1038/emi.2014.53

www.nature.com/emi

ORIGINAL ARTICLE

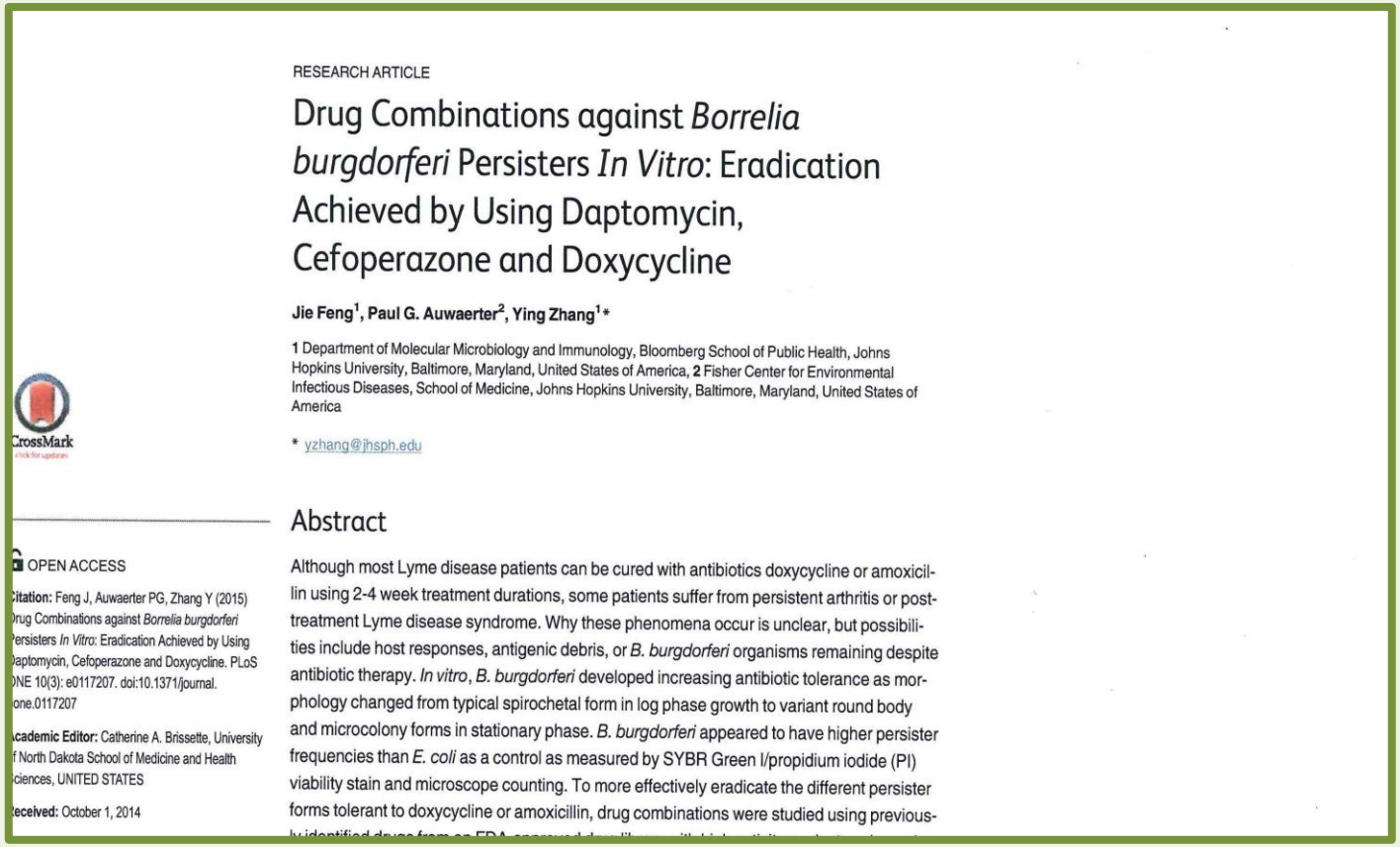
Identification of novel activity against *Borrelia burgdorferi* persisters using an FDA approved drug library

Jie Feng[1], Ting Wang[1], Wanliang Shi[1], Shuo Zhang[1], David Sullivan[1], Paul G Auwaerter[2] and Ying Zhang[1]

Although antibiotic treatment for Lyme disease is effective in the majority of cases, especially during the early phase of the disease, a minority of patients suffer from post-treatment Lyme disease syndrome (PTLDS). It is unclear what mechanisms drive this problem, and although slow or ineffective killing of *Borrelia burgdorferi* has been suggested as an explanation, there is a lack of evidence that viable organisms are present in PTLDS. Although not a clinical surrogate, insight may be gained by examining stationary-phase *in vitro Borrelia burgdorferi* persisters that survive treatment with the antibiotics doxycycline and amoxicillin. To identify drug candidates that can eliminate *B. burgdorferi* persisters more effectively, we screened an Food and Drug Administration (FDA)-approved drug library consisting of 1524 compounds against stationary-phase *B. burgdorferi* by using a newly developed high throughput SYBR Green I/propidium iodide (PI) assay. We identified 165 agents approved for use in other disease conditions that had more activity than doxycycline and amoxicillin against *B. burgdorferi* persisters. The top 27 drug candidates from the 165 hits were confirmed to have higher anti-persister activity than the current frontline antibiotics. Among the top 27 confirmed drug candidates from the 165 hits, daptomycin, clofazimine, carbomycin, sulfa drugs (e.g., sulfamethoxazole), and certain cephalosporins (e.g. cefoperazone) had the highest anti-persister activity. In addition, some drug candidates, such as daptomycin and clofazimine (which had the highest activity against non-growing persisters), had relatively poor activity or a high minimal inhibitory concentration (MIC) against growing *B. burgdorferi*. Our findings may have implications for the development of a more effective treatment for Lyme disease and for the relief of long-term symptoms that afflict some Lyme disease patients.
Emerging Microbes and Infections (2014) **3**, e49; doi:10.1038/emi.2014.53; published online 2 July 2014

Keywords: *Borrelia burgdorferi*; drug discovery; FDA approved drug library; persisters; SYBR Green I

Antibiotikakombinationen gegen Borrelia burgdorferi-Persiterformen



RESEARCH ARTICLE

Drug Combinations against *Borrelia burgdorferi* Persisters *In Vitro*: Eradication Achieved by Using Daptomycin, Cefoperazone and Doxycycline

Jie Feng[1], Paul G. Auwaerter[2], Ying Zhang[1]*

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OPEN ACCESS

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Academic Editor: Catherine A. Brissette, University of North Dakota School of Medicine and Health Sciences, UNITED STATES

Received: October 1, 2014

Abstract

Although most Lyme disease patients can be cured with antibiotics doxycycline or amoxicillin using 2-4 week treatment durations, some patients suffer from persistent arthritis or post-treatment Lyme disease syndrome. Why these phenomena occur is unclear, but possibilities include host responses, antigenic debris, or *B. burgdorferi* organisms remaining despite antibiotic therapy. *In vitro*, *B. burgdorferi* developed increasing antibiotic tolerance as morphology changed from typical spirochetal form in log phase growth to variant round body and microcolony forms in stationary phase. *B. burgdorferi* appeared to have higher persister frequencies than *E. coli* as a control as measured by SYBR Green I/propidium iodide (PI) viability stain and microscope counting. To more effectively eradicate the different persister forms tolerant to doxycycline or amoxicillin, drug combinations were studied using previous-

Langzeit-Antibiotikatherapie: Studien

- Bayer ME, Zhang L, Bayer MH. Borrelia burgdorferi DNA in the urine of treated patients with chronic Lyme disease symptoms. A PCR study of 97 cases. Infection 1996; 24 No.5.
- Cameron, DJ. Lyme Disease Clinical Trial - Effectiveness of Retreatment on Health-Related Quality of Life. Abstract, Lyme & Other TBDs: Emerging Tick Borne Diseases, Fri Oct 28th, 2005, Philadelphia, PA.
- Cimmino MA, Accardo S. Long term treatment of chronic Lyme arthritis with Benzathine penicillin. Ann Rheum Dis 1992 Aug; 51(8):1007-8.
- Cimmino MA, Moggiana GI, Parisi M, Accardo S. Treatment of Lyme arthritis. Infection 1996 Jan-Feb; 24(1):91-3.
- Cimperman J, Maraspin V, Lotric-Furlan S, Ruzic-Sabljic E, Strle F. Lyme meningitis: a one-year follow up controlled study. Wien Klin Wochenschr 1999; 111(22-23):961-3.

- Cimmino MA, Moggiana GI, Parisi M, Accardo S. Treatment of Lyme arthritis. Infection 1996 Jan-Feb; 24(1):91-3.

Langzeit-Antibiotikatherapie: Studien

- Dattwyler RJ, Volkman DJ, Luft BJ, Halperin JJ, Thomas J, Golightly MG. Seronegative Lyme disease. Dissociation of specific T- and B-lymphocyte responses to Borrelia burgdorferi. N Engl J Med 1988 Dec 1; 319(22):1441-6.
- Donta ST. Tetracycline therapy for chronic Lyme disease. Clin Infect Dis 1997; 25 Suppl 1:pS52-6.
- Fallon BA et al. Repeated antibiotic treatment in chronic Lyme disease. J Spirochet Tick Borne Dis, 1999 Fall/Winter:p94-101.
- Fallon BA et al. A randomized, placebo-controlled trial of repeated IV antibiotic therapy for Lyme encephalopathy. Neurology, 2007.
- Gasser R, Reisinger E, Eber B, Pokan R, Seinost G, Bergloff J, Horwarth R, Sedaj B, Klein W. Cases of Lyme borreliosis resistant to conventional treatment: improved symptoms with cephalosporin plus specific beta-lactamase inhibition. Microb Drug Resist 1995 Winter; 1(4):341-4.
- Georgilis K, Peacocke M, Klempner MS. Fibroblasts protect the Lyme disease spirochete, Borrelia burgdorferi, from ceftriaxone in vitro. J Infect Dis 1992 Aug; 166(2):440-4.

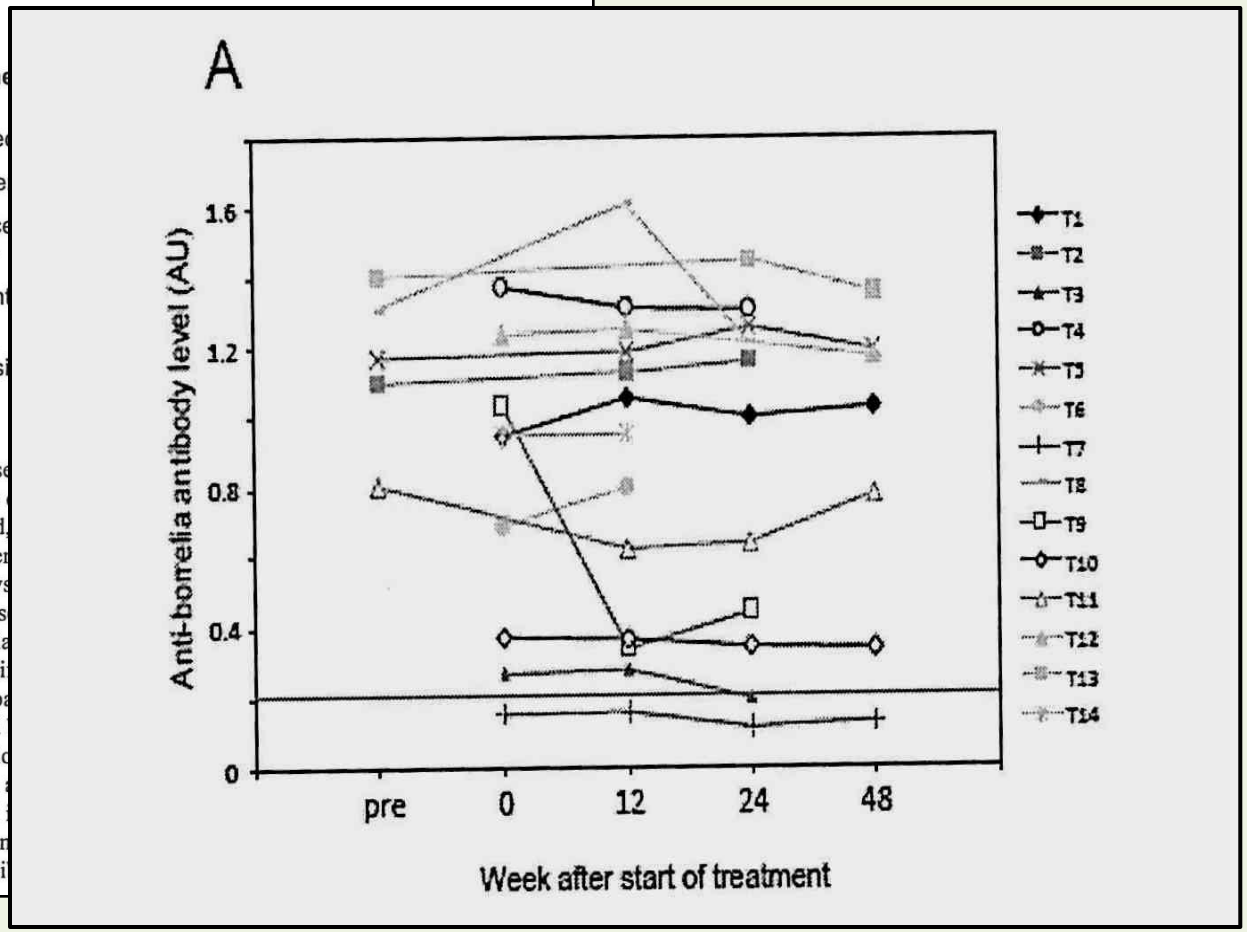
Therapiemonitoring durch Bestimmung der Antikörpertiter? – Nein!

Increased IFNα Activity and Differential Antibody Response in Patients with a History of Lyme Disease and Persistent Cognitive Deficits

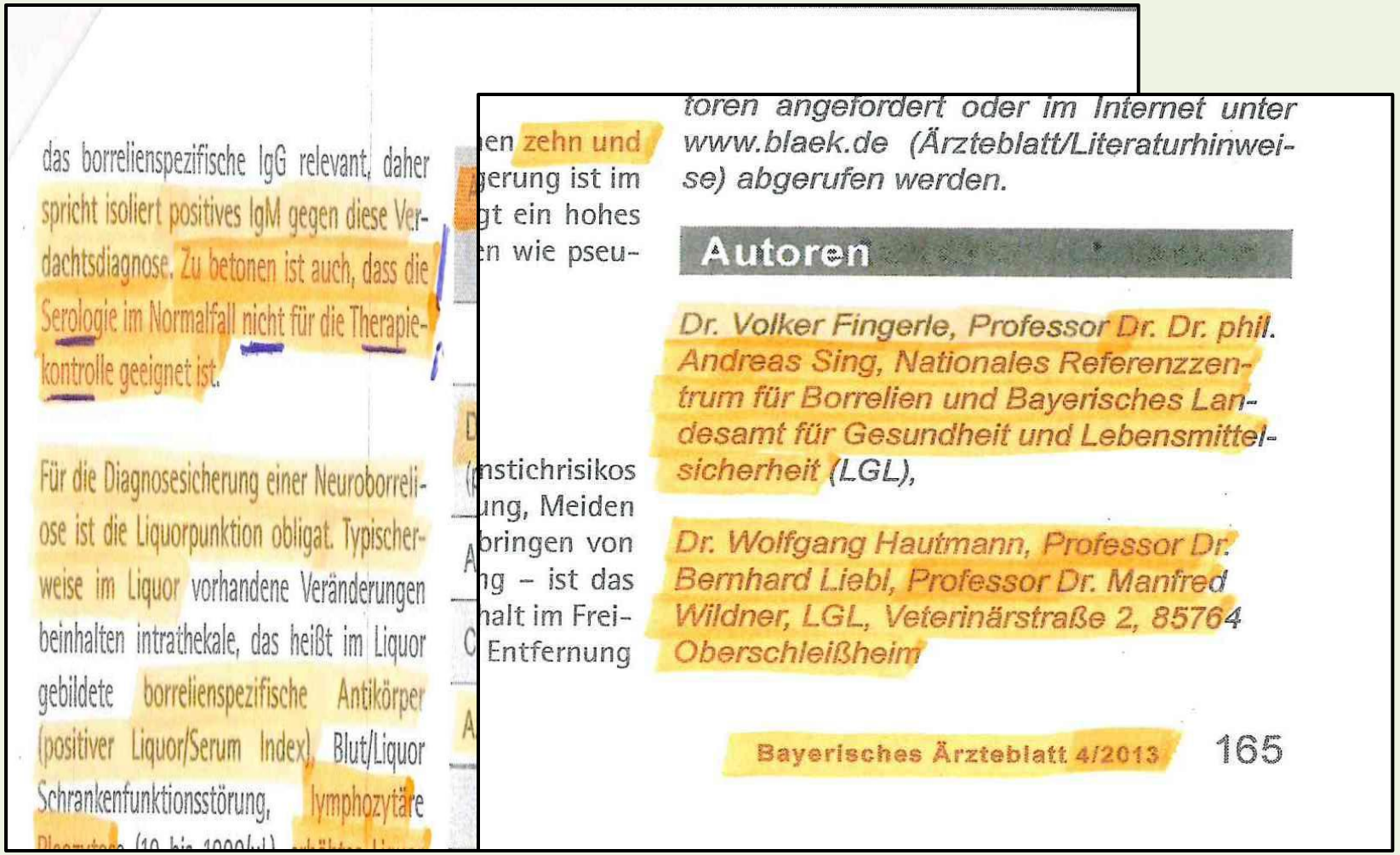
Elzbieta Jacek[a], **Brian A. Fallon**[b], **Abhishe**
and **Armin Alaedini**[e,*]
[a]Division of Rheumatology, Hospital for Spe
[b]Department of Psychiatry , Columbia Unive
[c]Department of Neurology and Neuroscience
York, NY, USA
[d]Division of Infectious Diseases, Departmen
NY, USA
[e]Department of Medicine, Columbia Universi

Abstract

Following antibiotic treatment for Lyme dise
symptoms of pain, fatigue, and/or cognitive
immune abnormalities, have been suggested
Furthermore, the effect of antibiotic treatme
unknown. In this study, a longitudinal analys
out in patients with a history of Lyme diseas
to and following treatment with either ceftria
detection of serum-induced changes in speci
and quantitative real-time PCR. Level and pa
Borrelia burgdorferi proteins were analyzed
cohort induced significantly higher expressio
healthy controls, indicating increased IFNα
borrelial proteins was significantly elevated
profile did not change significantly in respon
implies enhanced immune stimulation, possi



Statement dazu vom NRZ für Borrelien in Deutschland



das borrelienspezifische IgG relevant, daher spricht isoliert positives IgM gegen diese Verdachtsdiagnose. Zu betonen ist auch, dass die Serologie im Normalfall nicht für die Therapiekontrolle geeignet ist.

Für die Diagnosesicherung einer Neuroborreliose ist die Liquorpunktion obligat. Typischerweise im Liquor vorhandene Veränderungen beinhalten intrathekale, das heißt im Liquor gebildete borrelienspezifische Antikörper (positiver Liquor/Serum Index), Blut/Liquor Schrankenfunktionsstörung, lymphozytäre

toren angefordert oder im Internet unter www.blaek.de (Ärzteblatt/Literaturhinweise) abgerufen werden.

Autoren

Dr. Volker Fingerle, Professor Dr. Dr. phil. Andreas Sing, Nationales Referenzzentrum für Borrelien und Bayerisches Landesamt für Gesundheit und Lebensmittelsicherheit (LGL),

Dr. Wolfgang Hautmann, Professor Dr. Bernhard Liebl, Professor Dr. Manfred Wildner, LGL, Veterinärstraße 2, 85764 Oberschleißheim

Was dann?: EliSpot (Interferon-Gamma-Test)

- **Der EliSpot**-Test ist eine Labormethode auf zellulärer Ebene zur Bestimmung einer Infektion mit Borrelien und verschiedenen Co-Erregern. Die erste Generation des enzymatischen EliSpots (Interferon-y-Test) liefert uns im Zusammenspiel mit der Bestimmung der CD3- und CD57-NK-Zellen wichtige Zusatzinformationen aus dem zellulären Immunsystem über die Infektion.

- Die EliSpot-Technik (TB-Spot) wurde 2011 von der FDA überprüft und zugelassen für die Diagnostik der Tuberkulose

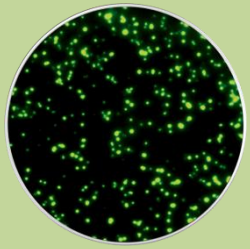
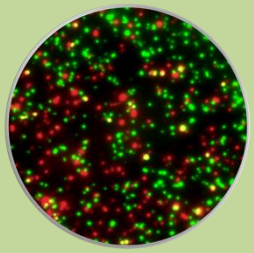
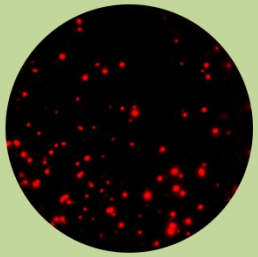
Studien dazu unter:
www.bca-clinic.de/Unsere Auffassung & Studien/Diagnostik/EliSpot (Interferon-Gamma-Test)

www.erlebnishaft.de/diagnostik/zelluläreabwehr

EliSpot: Die nächste Generation „LymeSpot revised“

- bietet detaillierte Aussage über **Aktivität der Infektion**
- Test differenziert in **aktive T-Effektor-Zellen** und **T-Memory-Zellen**, d.h. es besteht die Möglichkeit zu unterscheiden, ob aktive Infektion oder/und Inflammation (Entzündung oder Autoimmunprozess) vorliegt
- in Zwischenphase entscheidend klinische Bild des Patienten
- zuverlässige Entscheidungshilfe für Therapeuten

LymeSpot: Prinzip

	IL2-Wert	Interferon-γ- Wert	Therapeutische Konsequenz
	niedrig	hoch	antibiotische bzw. anti-infektive Therapie notwendig
			Entscheidung in Zusammenschau mit der klinischen Symptomatik (Antibiose weiter?)
	hoch	niedrig	Antibiotika-Therapie beenden. Bestehen weiter Symptome, nur Behandlung der Inflammation nötig

frontiers in
MICROBIOLOGY

ORIGINAL RESEARCH ARTICLE
published: 12 February 2015
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Specific *in vitro* interferon-gamma and IL-2 production as biomarkers during treatment of chronic Q fever

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Background: Antibiotic treatment of chronic Q fever is cumbersome and of long duration. To monitor treatment, there is a need for alternative biomarkers. *Coxiella burnetii*-specific interferon (IFN)-γ and interleukin (IL)-2 production reflect the type of effector and memory T-cell response. In chronic Q fever, *C. burnetii*-specific IFN-γ production is higher and IL-2 production is lower than in individuals with past Q fever. Here we explore whether *C. burnetii*-specific IFN-γ and IL-2 production correlate to treatment response.

Methods: We studied the longitudinal *C. burnetii*-specific IFN-γ/IL-2 ratio in fifteen proven chronic Q fever patients. All patients were followed for at least 18 months during antibiotic treatment. Treatment was considered successful when clinical recovery was observed, a positive PCR for *C. burnetii* DNA in blood became persistently negative, anti-phase I IgG showed a fourfold decrease or more, and imaging techniques showed disappearance of infectious foci.

Results: Overall, the IFN-γ/IL-2 ratio declined when patients experienced a successful treatment outcome. When treatment failed, IFN-γ/IL-2 ratios did not significantly decrease. The median (±IQR) slope of the longitudinal IFN-γ/IL-2 ratio with successful treatment was −2.10 (−7.02 to −0.06), and −0.15 (−1.13 to 0.25) with unsuccessful treatment ($P = 0.19$). Q fever endocarditis patients had higher IFN-γ/IL-2 ratios than patients with endovascular infections.

Conclusion: We propose that the IFN-γ/IL-2 ratio can be used as an additional biomarker for monitoring chronic Q fever treatment, with declining ratios being indicative of successful treatment.

Keywords: Q fever, *Coxiella burnetii*, cell-mediated immunity, interferon-gamma, interleukin-2, biomarker, serology, treatment

Schmerztherapie

Neben der ursächlichen Therapie hat die Schmerztherapie bei der Behandlung der Borreliose und anderer Zecken-übertragener Erkrankungen eine besondere Bedeutung. Ein gezieltes „Schmerzmanagement“ ist bei vielen Patienten erforderlich und sollte immer Bestandteil der Therapie sein.

Schmerz ist ein starker **Stressfaktor** und damit **ungünstig** für das. **Immunsystem (Stress---Produktion von Adrenalin und Cortisol).**

Häufige Schmerzformen bei Borreliose:

Muskuloskeletale Schmerzen :

- Arthritiden
- Polyarthralgien
- Myalgien

Neuropathische Schmerzen :

- Polyneuropathien
- Mono- und Polyneuritiden
- Neuralgien

Schmerztherapie

Zentrale Schmerzen :

- Meningitis
- Meningoradikuloneuritis

Behandlung nach dem Stufenschema der WHO:

WHO Stufe I

- Nicht-Opioid (z.B. Paracetamol, Ibuprofen, Diclofenac, Metamizol, COX-2-Hemmer)

WHO Stufe II

- schwaches Opioid (Tramadol, Tilidin-Naloxon, Dihydrocodein ret.) + Nicht-Opioid

WHO Stufe III

- starkes Opioid (Morphium, Hydromorphon, Fentanyl ?) + Nicht-Opioid

Schmerztherapie

Begleitmedikation in der Schmerztherapie „Co-Analgetika“:

- Antidepressiva (Amitriptylin, Doxepin)
- Antikonvulsiva (Carbamazepin, Gabapentin, Pregabalin)
- Sedativa (Lorazepam, Midazolam)
- Spasmolytika (Butylscopolamin)
- Antiemetika (Metoclopramid, Haloperidol)

Begleittherapie in der Schmerztherapie , physikalische Therapie :

- Elektro-Therapie
- Tens
- Akupunktur

Antibiose und Schmerzen Herxheimer-Reaktion

- Lungenentzündung, Hirnhautentzündung und Sepsis gehören zu den besonders gefürchteten Erkrankungen. Alle diese Krankheiten haben eines gemeinsam: Sie können von **Gram-negativen** Bakterien ausgelöst werden.
- Auch Borrelien-, Ehrlichien-, Chlamydien-, Bartonellen-, Yersinien-, Rickettsien-Stämme usw. sind **Gram-negative** Bakterien.
- Forscher haben jetzt gezeigt, dass die von diesen Bakterien erzeugten Giftstoffe (**LPS**) eine **direkte** Ursache für starke **Schmerzen** und auch **Entzündungen** sein können.

Antibiose und Schmerzen Herxheimer-Reaktion

- Die Zellwände der **Gram-negativen** Bakterien werden von Lipopolysacchariden (**LPS**), fetthaltigen Zuckerkettenmolekülen, stabilisiert. Werden die Bakterien nun vom **Immunsystem oder von Antibiotika** angegriffen, zerfallen sie und setzen große Mengen der **LPS** frei. In der Regel wirken die LPS als Signalstoffe und aktivieren die Zellen des Immunsystems.

- Ein europäisches Forscherteam aus Alicante, Leuven und Erlangen, an dem auch eine Arbeitsgruppe um Prof. Dr. Peter Reeh vom Institut für Physiologie und Pathophysiologie der FAU Nürnberg-Erlangen beteiligt ist, hat entdeckt, dass **LPS** auch die **direkte** Ursache für **Schmerzen** sein können. Sie sind in der Lage, **Nozizeptoren** – feine Nervenverästelungen, die Schmerz erzeugen können – zu aktivieren und zu sensibilisieren.

Herxheimer Reaktion

Verantwortlich für die leichte Erregbarkeit der Nervenfasern ist wiederum ein höchst universeller Chemorezeptor – das Eiweißmolekül TRPA1. Es handelt sich dabei um einen Ionenkanal, der in der Zellwand sitzt. Durch diesen Kanal strömen Ionen ein, die die Nerven erregen. Die Folge davon kennt jeder, der schon einmal Zwiebeln geschnitten hat: Der TRPA1 spricht auf den Schadstoff, das „Tränengas“, an und verursacht das unangenehme Brennen in Augen und Nase.

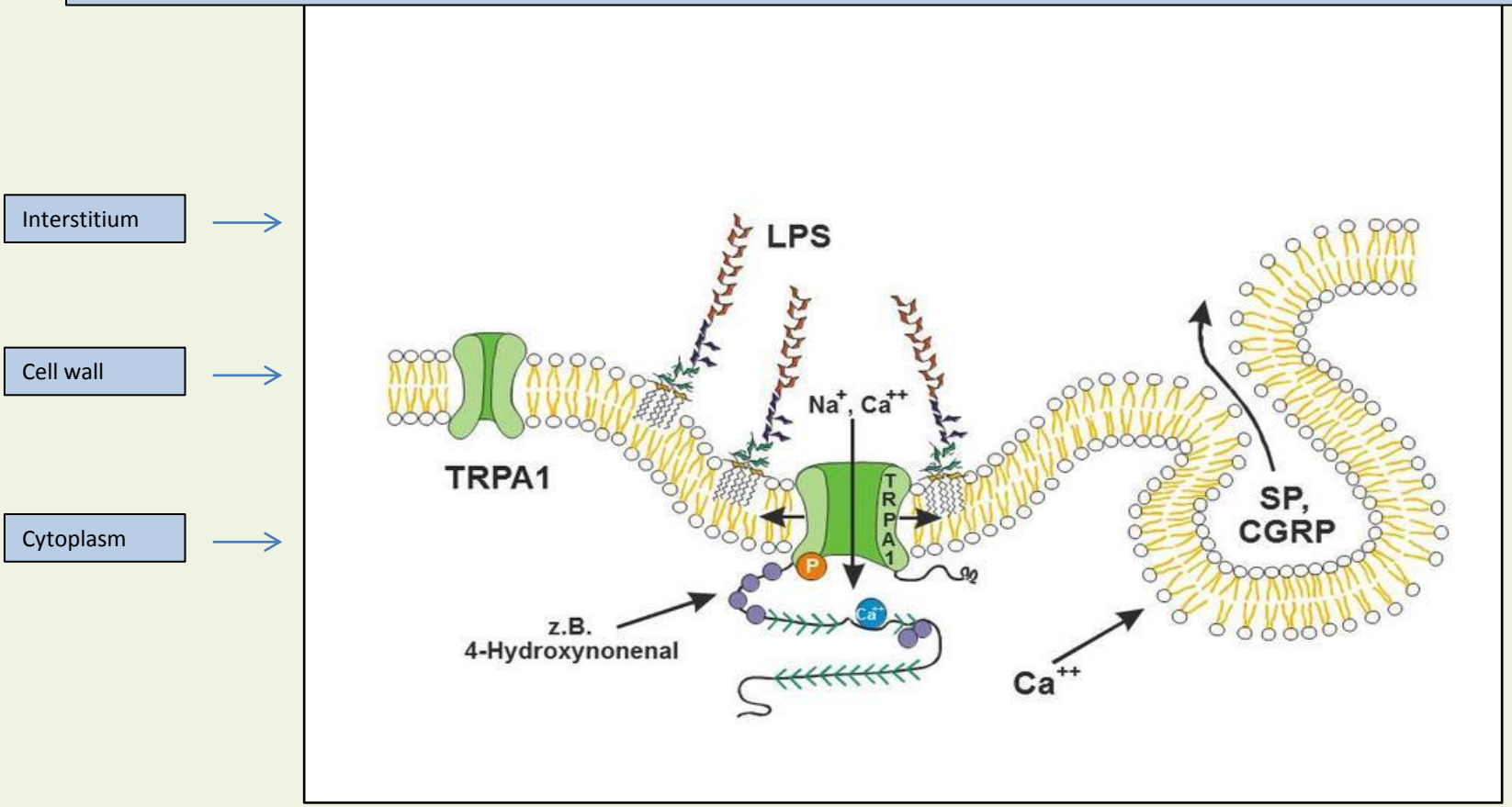
Zusammenfassung:

Mechanismus: Borrelien, Chlamydien, Ehrlichien und/oder andere **Gram-negative** Bakterien werden durch Antibiotika zerstört . Dadurch wird **LPS** freigesetzt, was wiederum zu **Schmerzen, Entzündungen, leichtem Fieber** und **Schwellungen** führen kann.

Das sind dann **keine allergischen Reaktionen**, sondern eine **Herxheimer Reaktion**. Das ist ein Hinweis für alle Therapeuten.

Gram-negative Bakterien, Antibiotika, LPS, Schmerz und mehr

Mechanism of operation in pain induction by LPS of Gram-negative bacteria



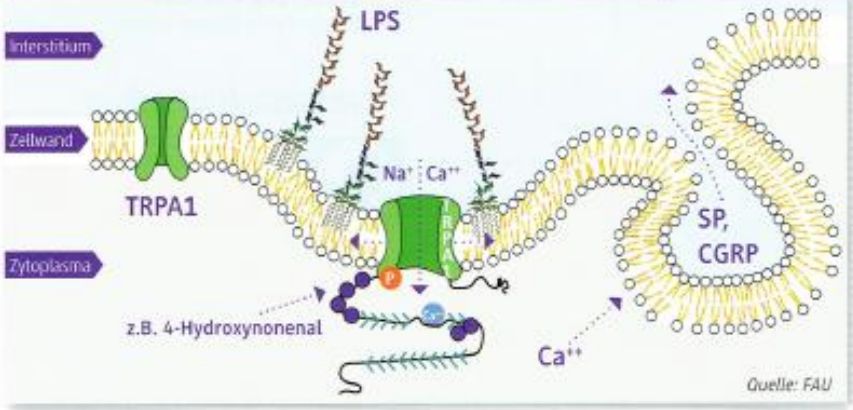
Antibiose und Schmerzen

WENN BAKTERIEN SCHMERZEN

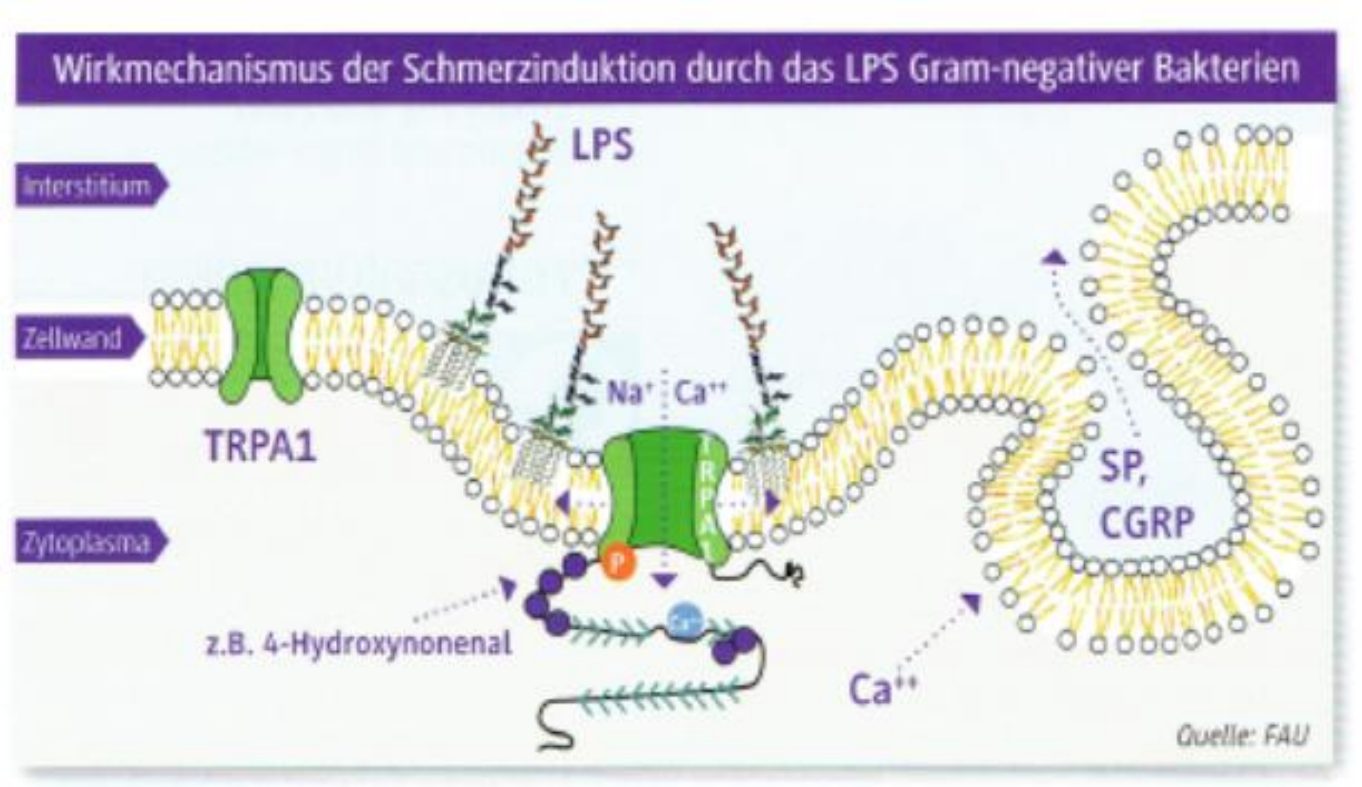
Lungenentzündung, Hirnhautentzündung und Sepsis haben eines gemeinsam: Sie können von sogenannten Gram-negativen Bakterien ausgelöst werden, zu denen auch viele Krankenhauskeime gehören. Die von diesen Bakterien erzeugten Giftstoffe können eine direkte Ursache für starke Schmerzen und Entzündungen sein. Die Zellwände der Gram-negativen Bakterien werden von Lipopolysacchariden (LPS), fetthaltigen Zuckerkettenmolekülen, stabilisiert. Werden die Bakterien nun vom Immunsystem oder von Antibiotika angegriffen, zerfallen sie und setzen große Mengen der LPS frei. In der Regel wirken die LPS als Signalstoffe und aktivieren die Zellen des Immunsystems. Ein europäisches Forscherteam unter Beteiligung der Arbeitsgruppe um Prof. Peter Reeh (Erlangen) hat entdeckt, dass LPS auch die direkte Ursache für Schmerzen sein können. Sie sind nämlich in der Lage, Nozizeptoren zu aktivieren und zu sensibilisieren. Verantwortlich für die leichte Erregbarkeit der Nervenfasern ist wiederum ein höchst universeller Chemorezeptor – das Eiweißmolekül TRPA1. Es handelt sich dabei um einen Ionenkanal in der Zellwand. Durch diesen Kanal strömen Ionen ein, die die Nerven erregen. Die Folge davon kennt jeder, der schon einmal Zwiebeln geschnitten hat: Der TRPA1 spricht auf den Schadstoff, das „Tränengas", an und verursacht das unangenehme Brennen in Augen und Nase. Durch den geöffneten Ionenkanal TRPA1 strömen Natrium- und Kalziumionen in die Nervenzellen ein und erregen diese. Die freigesetzten Neuropeptide (SP, CGRP) fördern schließlich die neurogene Entzündung. Red.

Pressemitteilung Friedrich-Alexander-Universität Erlangen-Nürnberg

Wirkmechanismus der Schmerzinduktion durch das LPS Gram-negativer Bakterien



Antibiose und Schmerzen



Behandlung der Borreliose und Ko-Infektionen

Vielen Dank für Ihre Aufmerksamkeit !

Besonderer Dank an Frau Prof. Dr. Leona Gilbert!
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