Pathomechanisms

of Borrelia burgdorferi sensu lato and their implications for diagnostics, clinical appearance and treatment of Lyme-Disease

Borrelia burgdorferi grows slowly

Bb needs ca. 12-20 (8-35) hours for one generation-time

- cf E. coli needs ca. 20 min for one generation-time
- Bb sometimes needs 10 weeks for culturing

1. Preac-Mursic et al, Infection 1996 Jan-Feb, 24 (1) 9-16; Kill kinetics of Bb and bacterial findings in relation to the treatment of LB
2. Hassler,http://www.dieterhassler.de/diagnostik_und_therapie.htm

The slow growing of Bb means for the infected human being:

- He / she can become ill a long time after infection (latency) [1]
- treatment has to take a long time to reach as many generations as in treatment of fast-growing-bacteria (60 -100 x?)
- Consider using therapy-principles of other slow-growing-bacteria; e.g. : M. leprae, M. tuberculosis, T. pallidum
  - treatment of TBC: combi for at least 6 months;
  - similar to leprosy: ca. 2 years combi-therapy (E. Freeksen, Borstel, Malta); before at least 10 years of Dapson [2]

1. Holger Blenk, Vorsitzender des Bundesverbandes der Ärzte für Mikrobiologie und Infektionsepidemiologe; Saarland online – 16 years latencywysi-wyg://19/http//www.sol.de/news/boulevard/fitness/139682.php3 :
2. Hans Schadewaldt, Über die Rückkehr der Seuchen; VGS Köln 1994, S. 68; Robugen

Borrelia burgdorferi sequester in tissue which is poorly vascularised

- connective tissue (present in all organs) and which is
- poorly infiltrated by defence cells - the immune system

Haupl, Burmester et al.: Persistence of Bb in ligamentous tissue from a patient with chronic LB; Arthritis Rheum 1993 Nov; 36(11): 1621-6

"Considering an early germ-dissemination into CNS .. it seems being necessary to reach high antibiotic-levels in target-tissues like joint-synovia or CNS.. even in treatment of erythema migrans or Borrelia-lymphozytom."

U. Neubert, Borreliosen – Therapie 1998, Fortschritte der praktischen Dermatologie und Venerolgie; ISBN 3-540-64352-4

"..In principle the disease symptoms result from the high affinity of the Borreliae to collagen fibre. Thus connective tissue (collagen) is particularly prone to chronic inflammatory processes. The result is vessel inflammation (vasculitis processes with perivascular infiltrates of lymphocytes and plasma cells) (literature: Meier, de Koning, Duray). Capillary occlusions lead to disturbances of the tissue-supply, e.g. the vessels by which nerves are supplied (Epineurium). This again leads to (ischaemia -) pain and increased vulnerability. So probably the periarticular decalcifying process is a consequence of the poor local supply in the bone. Borreliae can probably partly evade the the immune system by sequestering in collagen where they are inaccessible to antibiotics ."

http://www.dieterhassler.de/diagnostik_und_therapie.htm

Decorin-binding-proteins (Dbp A, DbpB) are thought to be adhesion-molecules of Bb to collagen-associated extracellular matrix (decorin)

1. Exner M., Successful vaccination for LD...; Expert Opin. Biol.Ther. (2001) 1(5): 783-793
2. Guo et al.: Mol.Microbiol (1998) 30:711-723 and Infect.Immun. (1995) 63:3467-3472

Borrelia burgdorferi is able to invade human cells and persist there:

e.g. blood-cells (macrophages), fibroblasts, endothelial, and synovial cells
Perhaps Bb can even survive in CNS-cells?

1. Malawista:J Immunol 1993 Feb1; 150(3) 909-15; Persistenz in Maus-Makrophagen
2. Ma Y, A Sturrock , JJ Weis: Intracellular localization of Borrelia burgdorferi within human endothelial cells. Infection and Immunity 59, 1991 671-678
3. Haupl, Burmester et al.: Persistence of Bb in ligamentous tissue from a patient with chronic LB; Arthritis Rheum 1993 Nov; 36(11): 1621-6
4. Arthritis Rheum 2001 Jan;44(1):151-62; Insights from a novel three-dimensional in vitro model of lyme arthritis: standardized analysis of cellular and molecular interactions between Borrelia burgdorferi and synovial explants and fibroblasts.Franz JK, Fritze O, Rittig M, Keysser G, Priem S, Zacher J, Burmester GR, Krause A.

Cell wall permeable antibiotics are required to treat intracellular Bb

- Tetracycline, Doxycycline, Minocycline
- Macrolides: Roxithromycin, Azithromycin, Clarithromycin, **- no Erythromycin!**

1. Hunfeld et al: Standardised in vitro susceptibility testing of Bb against well-known and newly developed antimicrobial agents - possible implications for new therapeutic approaches to LD; Int.Med.Microbiol.291; Suppl.33, 125-137 (2002)
2. Terekhova, Antimicrobial Agents and Chemotherapy, Nov 2002, p.3637-3640, Vol.46, No.11; Erythromycin Resistance in Bb

Borrelia burgdorferi can change its appearance

- by "starvation" (antibiotics, CSF) Bb can change its appearance:
  - cyst, bleb, mesosom, granulum
- a "cyst" / L-form / spheroblast can later convert to living spirochetes again

1. Brorson; Infection 1997 Jul-Aug 25(4) 240-6, Transformation of cystic forms of Borrelia burgdorferi to normal, mobile spirochetes.
2. Kersten; Antimicrobial Agents and Chemotherapie; May 1995; p.1127-1133: Effects of Penicillin, Ceftriaxon and Doxycycline on Morphology of Bb
3. Gruntar, Cinco: APMIS 2001 May; 109(5): 383-8; Conversion of B. garinii cystic forms to motile spirochetes in vivo
4. Brorson, O., & Brorson S, Infection, 1998;26(3):144-50 (R) In vitro conversion of Borrelia burgdorferi to cystic forms in spinal fluid, and transformation to mobile spirochetes by incubation in BSK-H medium.

"Cysts" are resistant to the usual antibiotics

- Metronidazole can be used against cysts
- CNS tissue is highly permeable to it
- Metronidazole can cause cancer or harm an embryo / foetus
- Possible to use other treatment options against cysts: Hydroxychloroquin (anti-malaria-drug); ranitidine bismuth citrate

1. Brorson; An in vitro study of the susceptibility of mobile and cystic forms of Bb to hydroxychloroquine; Int Microbiol 2002 Mar;5 (1) :25-31
2. Brorson: Brorson O, Brorson SH, APMIS 1999 Jun; 107 (6): 566-76, An in vitro study of the susceptibility of mobile and cystic forms of Borrelia burgdorferi to Metronidazole
3. Brorson; Int.Microbiol 2001 Dec; 4(4):209-15; Susceptibility of motile and cystic forms of Bb to rantidine bismuth citrate