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Chronic Persistent Infection in Lyme Neuroborreliosis Despite Prior Intensive Antibiotic Treatment – Challenge to Duration of Treatment for Late Neurologic Lyme Disease and Post-Lyme Syndromes.

CONTESTED RECOMMENDATIONS:

“Post-Lyme disease syndrome, posttreatment chronic Lyme disease, and chronic Lyme disease”.

Recommendation 2, Page 1120-1121:

*“To date, there is no convincing biologic evidence for the existence of symptomatic chronic *B. burgdorferi* infection among patients after receipt of recommended treatment regimens for Lyme disease. Antibiotic therapy has not proven to be useful and is not recommended for patients with chronic (>6 months) subjective symptoms after administration of recommended treatment regimens for Lyme disease.”¹*

and:

“Late Neurologic Lyme Disease”

Recommendation 3, Page 1113:

“Adult patients with late neurologic disease affecting the central or peripheral nervous system should be treated with ceftriaxone (2 g once per day intravenously for 2-4 weeks)(tables 2 and 3)(BII). Cefotaxime or penicillin G administered intravenously is an alternative (BII). Response to treatment is usually slow and may be incomplete. Re-treatment is not recommended unless relapse is shown by reliable objective measures.”¹

EVIDENCE TO CONTEST IDSA RECOMMENDATIONS:

B. burgdorferi was cultured at the Centers for Disease Control in Fort Collins, Colorado from cerebrospinal fluid obtained December 1991 from one of my patients after treatment with putatively curative intravenous [cefotaxime 2 grams IV Q 8 hr. X 21 days] and oral antibiotics [minocycline 200 mg P.O. QD X 4 months]². This was reported with colleagues from the CDC in an abstract presented at the Vth International Conference on Lyme Borreliosis held in Alexandria, Virginia³ and on the front page of the Reporter Dispatch, a Westchester county publication⁴ and in the New York Times Science Times⁵. The case prompted me to write a Guest Commentary for the Journal of Clinical Microbiology⁶. Full details of the case were later published in the Journal of Spirochetal and Tick-borne Diseases⁷. The patient was immunocompromised by virtue of prior splenectomy. Pleocytosis which had been present for several years and which failed to resolve with 21 days of cefotaxime IV resolved completely with 13 weeks of weekly “pulsed” high dose treatment with the same drug.

It is noteworthy that the patient was seronegative for Lyme disease until 12/91 despite some 4 years of clinical illness and showed variable seroreactivity thereafter.

After an hiatus in treatment she developed a pleuropericardial effusion and required the creation of a pericardial window to prevent pericardial tamponade and for diagnostic purposes. The pericardium showed pericarditis with lymphocytes and plasma cells on hematoxylin and eosin staining and touch preparation showed a borrelia-compatible structure⁷.

Thereafter she benefited in objectively verifiable ways from re-treatment with intravenous antibiotics whenever an adequate duration of 3-6 months of therapy could be applied (e.g. objective improvement in neuropsychological testing or distance she could traverse with a rolling walker).

This case is incontrovertible proof of the reality of symptomatic persisting infection in a **North American** case of Lyme borreliosis following application of intensive antibiotic treatment exceeding recommended guidelines. The Centers for Disease Control and Prevention sought and received a unit donation of serum from this patient for use as a positive control in their Lyme disease reference serum bank.

When it became non-feasible for extended intravenous antibiotic therapy to be periodically reinstated the patient insidiously deteriorated. She died July 17, 2003 following a myocardial infarction which had ensued after a series of grand mal seizures.

I have the consent of the patient, Vicki Logan⁸ and her sole surviving next of kin⁹ to release the autopsy findings¹⁰. This disclosed cerebral vasculitis with prominence of plasma cells in vessel walls¹¹.

Immunohistochemistry performed by Klaus Eisendle using methods he has described applied to skin in well-characterized patients with Lyme disease¹² showed uptake within vessel walls in proximity to plasma cells¹³. The case is under further study and has not yet been submitted for publication.

Another fatal case reported in detail in my article in the Journal of Spirochetal and Tick-borne Diseases demonstrated spirochetal-compatible structures on electron microscopy and was positive by PCR for detection of Lyme DNA in both brain and meningeal tissue despite prior application of intensive and prolonged intravenous antibiotic therapy⁷.

A fatal case of encephalitis in a Connecticut child following an untreated engorged deer tick bite was reported as an abstract appearing in the VIII International Conference on Lyme Borreliosis in Munich, Germany¹⁴. Although seriously neurologically damaged, the patient was improving until intravenous antibiotic treatment had to be discontinued. The patient subsequently deteriorated and died with intractable seizures. An autopsy was performed on the child. Health authorities declined to study the case.

I have also reported the case of a patient with recurrent erythema migrans despite a prior prolonged course of oral antibiotic therapy in which a spirochetal-compatible structure was identified by silver staining in a skin biopsy¹⁵. This patient had virtually no opportunity for additional tick exposure.

In the early 1990s colleagues at the Centers for Disease Control asked me to forward to them samples of urine and serum from patients who were under evaluation for possible Lyme disease. Unbeknownst to me, CDC forwarded these specimens on to the Rocky Mountain Laboratory of the National Institute for Allergy and Infectious Diseases for study by Dr. Claude Garon, Ph.D., then Chief of the Microscopy section, and his colleague David Doward, Ph.D. They had done fundamental work on the biology of *B. burgdorferi* which they published in the journal Scanning Microscopy¹⁶. They devised a method using electron microscopy for detecting blebs shed by the outer membrane of Lyme spirochetes by immunogold staining¹⁷. Drs. Garon and Doward prepared a chart comparing the results of the RML urine antigen test versus standard ELISA methods in serum¹⁸ and the results of

testing on my patients was also reported at the V International Conference on Lyme Borreliosis¹⁹. Their work demonstrated that many patients testing negative on standard serologic methods tested positive on direct antigen detection using their method in urine. These patients had an impressive diversity of clinical presentations. One, who gave a history of an eruption historically compatible with erythema migrans, died of pulmonary hypertension. Unfortunately, an autopsy was not performed.

The test method of Garon and Dorward was heralded in an article in the Health Section of the New York Times²⁰. Unfortunately, their method has languished and has never been used further on either a research basis or commercially for clinical diagnostic purposes. Their work does reveal that there is a deep complexity to Lyme disease such that presently available methods do not begin to scratch the surface of the biologic reality of the disease.

In 2002 I had the opportunity to send 129 specimens of frozen cerebrospinal fluid from 108 patients to the research laboratory of Dr. Raymond Dattwyler at SUNY Stony Brook for application of special methods of testing. These included antigen capture assays for Outer surface proteins A (OspA) and C (OspC) and IgG and IgM borrelia-specific immune complexes. These test methods had been studied and developed by Dr. Steven Schutzer^{21,22,23} and Dr. Patricia Coyle^{24,25}. The methodology of this CDC-funded research involved sharing aliquots of research specimens between three different collaborating laboratories and found good reproducibility according to the Research Coordinator who administered the project. The results in my patients showed that some 79 of 129 specimens (61%) tested positive on one or more of the 4 research assays whereas standard tests for Lyme disease on the same CSF specimens were negative in all but 3 specimens for a yield of just 2%²⁶. I did not feel it was my role to publish these results on my patients for research assays to which I happened to gain access fortuitously. I suspect that the findings on my patients must not have been unique but to the best of my knowledge the results of the studies carried out at the research laboratory of Dr. Dattwyler and the other two collaborating research groups during that time frame have never been published.

Incidentally the specimens submitted included serial specimens of CSF on Vicki Logan. All of these tested positive on one or more of the research assays from Dr. Dattwyler's research laboratory, the last and most recent aliquot being tested showing positive results for OspC antigen detection at a magnitude 7 times greater than the positive cut-off²⁷. Once again, cutting edge methods suggest there is a deeper reality operative in Lyme disease patients than is apparent using currently commercially available methods of testing.

It is difficult to prove persistence of infection after recommended treatment of Lyme disease because the tools we have at our disposal are presently limited and such cases require

intensive and determined study. Few pathologists in the United States are trained to evaluate human tissues for evidence of Lyme disease or determined enough to undertake the kind of meticulous and exhaustive search necessary to unravel the complexities of the illness. That *published* reports of such cases in Lyme disease are relatively few in number does not necessarily mean that they occur only rarely; rather our means to prove it conclusively are not readily available to clinicians. Additionally, clinicians' attempts to report their experience with chronic and neurologic Lyme disease have been suppressed by editorial review boards²⁸ and conference organizers²⁹.

There are, nonetheless extensive studies in the worldwide peer-reviewed literature in both humans and animals which corroborate persistence of borrelial infection despite prior antibiotic treatment³⁰⁻³⁶. Additional studies *in vitro* demonstrate convincingly that the Lyme organism has the capacity to invade, persist in, resist the action of antibiotics while in an intracellular location and to be viable following liberation from intracellular sites^{37,38}.

To maintain that an organism which demonstrates such capacity *in vitro* may not be able to utilize applicable mechanisms *in vivo* is disingenuous and such a contention itself is actually highly implausible. In fact, when suitable research tools have been applied to clinical material such intracellular localization *has* been demonstrated³⁹.

It is also crucial to realize that treatment failure after application of intensive antibiotic therapy has been reported for syphilis, another spirochetal infection, in persons with impaired immune status as well as in immunocompetent individuals⁴⁰⁻⁵⁰. The well-accepted practice of following persons who have been treated for syphilis for surveillance purposes reflects the wide recognition within the medical profession that this illness has the potential to relapse despite prior treatment. Furthermore, if neurologic symptoms occur in such persons and if no other plausible cause of the symptoms is evident after careful evaluation, the dictum is to treat further with antibiotics⁵¹⁻⁵³. Whereas the authors of the 2006 IDSA Lyme disease guidelines maintain it is “biologically implausible” for Lyme spirochetes to survive despite prior treatment with antibiotics, actually there is ample precedent for this phenomenon in syphilis.

Necessary is a profound commitment to the proper pathologic study of Lyme disease in humans using all known methods^{54,55} as well as support for the development and widespread clinical availability of the type of new and improved direct detection methodologies^{17,21,24,25} to which I was fortunate to have access.

Science demands that all available information be evaluated in trying to approximate the truth not just evidence that supports one point of view. Failure to consider all of the


relevant evidence concerning chronic Lyme disease violates fundamental principles of inductive reasoning central to dispassionate and objective scientific inquiry⁵⁶ and impedes scientific progress.

General reassessment of all that is assumed to be true about Lyme disease is needed including its chronic manifestations. The work of this panel constitutes a vital and necessary component of that reassessment.

I urge the review panel in the strongest possible terms to reject categorically the position taken by the authors of the 2006 IDSA Guidelines on Lyme disease that “to date, there is no convincing biologic evidence for the existence of symptomatic chronic *B. burgdorferi* infection among patients after receipt of recommended treatment regimens for Lyme disease” and that “Antibiotic therapy has not proven to be useful and is not recommended for patients with chronic (>6 months) subjective symptoms after administration of recommended treatment regimens for Lyme disease”. Rejected also should be the section on Late Neurologic Lyme disease limiting initial treatment to 2-4 weeks of intravenous ceftriaxone, cefotaxime or penicillin G and discouraging re-treatment in the absence of reliable objective measures of relapse.

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(Note: all listed articles and exhibits are included in separate binder for Kenneth Liegner, M.D.)

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8. Consent from patient for disclosure of information.
9. Consent from patient's sole next of kin for disclosure of information.
10. Autopsy report from Departments of Pathology and Neuropathology, Columbia Presbyterian Hospital Medical Center.
11. Photomicrograph, hematoxylin & eosin of cerebral vessel with lymphoplasmacytic vasculitis (Klaus Eisendle, M.D.,Ph.D.)
12. Eisendle K, Grabner T, Zelger B. Focus Floating Microscopy "Gold Standard" for Cutaneous Borreliosis? American Journal of Clinical Pathology. 2007;127:213-222.
13. Photomicrograph showing immunohistochemical uptake in structures in proximity of cerebral lymphoplasmacytic vasculitis (Klaus Eisendle, M.D.,Ph.D.)
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26. Print-out of results of research assays versus standard assays on 129 frozen CSF specimens from 108 patients from Dr. Liegner's practice performed 2002 in the research laboratory of Dr. Raymond Dattwyler at SUNY Stony Brook by Priscilla Munoz, Laboratory Supervisor, Research Coordinator and Administrator. Names of all patients except Vicki Logan are redacted. **All positive results are highlighted in yellow.**
27. Reports of results of research assays from Dr. Dattwyler's Research Laboratory on Vicki Logan's CSF samples from 7/6/99, 9/18/2000 and 6/20/2001.
28. Correspondence from Sidney M. Finegold, M.D., Editor of Clinical Infectious Diseases concerning submission of manuscript "Lyme Disease and the Clinical Spectrum of Antibiotic Responsive Meningoencephalo-myelitides"; note abrupt shift from generally encouraging reviews including one highly favorable on initial review to surprising across the board rejection upon re-review after revision. The one strongly favorable reviewer is inexplicably dropped from the review process.
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