Marzec, et al (1) described 5 cases of treated chronic Lyme disease that resulted in poor outcomes We are concerned about 3 conclusions: 1. Characterization of chronic Lyme disease as an invalid nebulous condition 2 “…..evidence that the recommended two-tiered serologic testing is actually more sensitive the longer *B. burgdeorferi* infection has been present” 3. “Studies have not shown that such treatments lead to substantial long-term improvements for patients.” We too are concerned about any individual whose outcomes represent complications to well-intentioned intervention. However, there is substantive support in the literature for the existence of 1. Chronic Lyme disease-Our perspective is that this represents the clinical manifestations of ongoing active infection by *Borrelia burgdorferi (Bb)* sensu latu complex in the setting of either chronic untreated or inadequately treated individuals. The lilkihood of undiagnosed acute Lyme is increased by the infrequency of patients recalling tick bites. In one study representing CDC criteria diagnosed Lyme disease, only 14% had that recollection. (2) Not all cases of acute Lyme are associated with an erythema (EM) rash. Over 15 years, 31% of the reported surveillance cases lacked an EM rash. (3) The ILADS guidelines (4) describe the Lyme post treatment "….persistence of *B. burgdorferi* in specific individuals and animal models." The 2012 Embers (5) nonhuman primate and 2014 Hodzic (6) murine studies provide evidence of persistence of *Bb* infection after MBC adequate courses of antimicrobials. Additional animal and human studies support this concept (7-10). We want to emphasize that other etiologies may be causal, but that a cohort of these patients likely have a perpetuation of chronic signs and symptoms due to an active *Bb* infection. 2. Sensitivity of two tiered testing in late Lyme: Based upon a 2008 study by Steere et al (11) “the sensitivity of 2-tier testing in patients with later manifestations of Lyme disease was 100%, and the specificity was 99%” Entrance criteria for late stage Lyme: “In all patients with neurologic, cardiac, or joint involvement, a serologic result positive for *B. burgdorferi* by ELISA and Western blot was required for case inclusion….” “Because the entrance criteria for the aforementioned analysis REQUIRED positive serologies … by definition, all patients with disseminated or persistent Lyme disease were required to

have a positive serologic test result. It is disingenuous to define a condition by a positive test result and then state that the test has 100% sensitivity…" (12)

By extension, the concept of seronegativity is well-documented in cases of chronic Lyme disease (13-15) In a study patients with positive cuture and/or pcr results and active late Lyme disease, 63.5% were not two-tier positive. (16) A second study of pcr positive late Lyme patients found that 56.3% were seronegative. (17)) 3. "Studies have not shown that such treatments lead to substantial long-term improvements for patients." A number of studies discount this claim. In 2 of the 4 NIH supported prospective human trials by Fallon (18) and Krupp (19), sub-cohort analysis showed statistically significant benefit to retreatment. In the former study 37 patients who were suspected of having active neuroborreliosis, and were treated with 10 weeks of 2gms/day IV Ceftriaxone. Pain and physical functioning improved at 12 and was sustained at 24 weeks. The authors indicated that "these benefits were felt to be independent of carefully assessed placebo effects." In the latter study 55 patients who were felt to have active infection by *Bb*, with persistent severe fatigue of 6 or more months received 28 days of IV Ceftriaxone. A significant improvement in fatigue was sustained at 6 months. Other prospective trials of prolonged antimicrobial treatment were employed that revealed statistically significant improved outcomes. (18-20) In summary, as unfortunate are the 5 cases reported by Marzec, it is this author's belief that they should not be used to discount a real entity, chronic Lyme disease. Whether due to the lack of timely diagnosis or adequacy of intervention, the literature supports the concept of chronic active Bb infection. That the diagnostic sensitivity of the 2 tiered paradigm is flawed, and seronegative active Bb infection exists. That emphasis should be made to generate a careful differential diagnosis, proactive management with probiotics and careful monitoring in the selective utility of long term antibiotics. As such, these often disabled individuals will more readily have access to the care they deserve, with compassion and empathetic oversight. Samuel Shor, MD, FACP President ILADS [International Lyme and Associated Diseases Society] Associate Clinical Professor George Washington University Health Care Sciences

1. <PMID:28617768>
2. <PMID:2814169>
3. <PMID:18830214>
4. <PMID:25077519>
5. <PMID:22253822>
6. <PMID:24466286>
7. <PMID:9818893>
8. <PMID:2345301>

9. <PMID:15369225>
10. <PMID:12160168>
11. <PMID:18532885>
12. <PMID:18800935>
13. <PMID:11251580>
14. <PMID:12189466>
15. <PMID:1967770>
16. <PMID:7494012>
17. <PMID:15068385>
18. <PMID:17928580>
19. <PMID:12821734>
20. <PMID:18971914>

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