Do Guidelines for Lupus Anticoagulant Testing Work in Practice?

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Nearly thirty years have passed since international guidelines related to the laboratory testing for the lupus anticoagulant (LA) were first introduced by a Working Party on Acquired Inhibitors of Coagulation for the International Society on Thrombosis and Haemostasis (ISTH). These guidelines were improved and modified in 1991 by the Subcommittee for the Standardization of Lupus Anticoagulants of the ISTH Scientific and Standardization Committee (SSC). In 1995, the newly named Subcommittee on Lupus Anticoagulant/Antiphospholipid Antibody of the ISTH SSC re-evaluated the 1991 guidelines and set forth four diagnostic criteria and eight recommendations for the laboratory diagnosis of LA. The points outlined in the 1995 guidelines were reiterated and enhanced by guidelines compiled by the British Committee for Standards in Haematology (BCSH) in 2000 and the College of American Pathologists (CAP) in 2002. The SSC 1995 guidelines were updated in 2009 and issues that were addressed or updated included: 1) patient selection, 2) specimen procurement and sample processing, 3) choice of assays (two screen tests of different principles and a confirmatory assay), 4) issues related to mixing tests, 5) interpretation of test results (significance of cut-off values), and 6) how results were to be reported (linking LA testing with other antiphospholipid testing). Presently the Clinical and Laboratory Standards Institute (CLSI) is in the process of preparing a LA guideline that will harmonize with previous global initiatives. Moreover it will attempt to build upon and clarify recommendations presented in the 2009 SSC guidelines and present the information in a succinct, practical, and easy to understand format.

Publications have directly addressed the issue of compliance or lack thereof with the aforementioned guidelines. Conformity to the BCSH guidelines was investigated by the United Kingdom National External Quality Assessment Scheme (UK NEQAS) in 2002 (Br J Haematol 2002;119:364-369). Approximately 63% of participants had testing strategies that were in compliance with the BCSH guidelines; however data from an external quality assessment (EQA) challenge showed a 30% false negative rate with a LA positive sample. An evaluation of practices (Thromb Haemost 2009;101:178-184) by participants from the North American Specialized Coagulation Laboratory Association (NASCOLA) and ECAT EQA program showed that >65% of laboratories complied with three of the four 1995 SSC criteria (use two or more tests based on different principles with low phospholipid concentrations to exclude LA; demonstrate inhibitory effect of patient plasma on normal pooled plasma, and confirm LA phospholipid dependency). Nonetheless, <35% complied with the fourth criterion which counsels evaluating for other coagulopathies that coexist or interfere with LA testing, before making a final laboratory diagnosis of LA. In 2008 and 2009 NASCOLA participants were challenged with five consecutive proficiency testing samples (four positive for LA and one negative for LA). The overall noncompliance rate (to 1995 SSC guidelines) ranged from 8% to 38% across proficiency testing periods and the majority of laboratories that were noncompliant failed to perform mixing tests. Intermediate to weak LA were misdiagnosed by nearly 25% of the participants and interestingly laboratories which were compliant with guidelines had substantial false-negative rates (16-24%), though rates were even higher (30-40%) if laboratories were noncompliant (Am J Clin Pathol 2010;134:764-773).

It is hoped that guidelines help in standardizing an approach to LA testing, gain acceptance in practice, and improve testing quality. Adherence or non-adherence to guidelines may

depend, in part, on availability of assays to a laboratory, financial constraints, and physician ordering practices. Additionally, the popularity (acceptance) of particular assays may drive their inclusion into guidelines though lesser known assays may be comparable or better. Clearance (approval) by governmental agencies for certain assays may drive the marketplace and create a potential for non-compliance to guidelines. Finally if guidelines are not clearly written, they tend to be used less or misinterpreted leading to more and not less confusion and by that non-compliance. However acceptance and utility may ultimately reside with EQA programs worldwide which can help answer a core question: is compliance with guidelines necessary for making a correct diagnosis of the LA?