INHIBITOR TESTING: POSITIVE OR NEGATIVE ? TRUE OR FALSE ?

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Broadly speaking, ‘inhibitors’ of coagulation can comprise either specific or non-specific inhibitors, and can be associated with either increased risk of thrombosis or of bleeding. Lupus anticoagulants (LA) are generally associated with thrombosis, whereas specific inhibitors of coagulation, directed against particular clotting factors, are typically associated with increased bleeding risk, or may otherwise compromise therapeutic support. Specific inhibitors may comprise allo-antibodies generated in congenitally deficient individuals (eg haemophilia A lacking factor VIII [FVIII]) or auto-antibodies in acquired cases of haemophilia. Assessment for these specific inhibitors initially comprises observation of abnormal routine coagulation test times (usually with the activated partial thromboplastin time; APTT) with failure of complete correction upon mixing with normal plasma. However, inhibitors to FVIII will typically show a time and temperature dependence, and so mixing studies may be misinterpreted.

Specific inhibitor testing can follow, with this normally comprising a Bethesda assay, or a modification thereof (usually using the Nijmegen method). The laboratory process for inhibitor testing is problematic, and there are traps for the unwary at each stage of the process. As mentioned, interpretation is not always straight-forward for coagulation mixing studies. For specific testing by Bethesda or Nijmegen modification, when asked, many labs may not even know which method they are using. There are issues with low level sensitivity, such that levels under 1 or 2 Bethesda Units (BU) may be clinically significant, but difficult to accurately determine. Even with high titre inhibitors, intra-laboratory variation can be as high as 50% or more. There are also problems with false positives and false negatives. The latter can arise when assessing a low-level inhibitor with an inferior methodology, and the former can arise in a multitude of situations. For example, false positives can occur when testing of LA, normal EDTA plasma, normal heparinized plasma, and even when testing warfarin or normal aged plasma.