NAME OF PROJECT

Update of the guidelines for lupus anticoagulant detection and interpretation

Subcommittee on Lupus anticoagulant / antiphospholipid antibodies

Person responsible (Chair / Principal Investigator): Katrien Devreese/Hannah Cohen

Investigators: Hannah Cohen, Katrien Devreese

Description Abstract

The update of the guidelines for lupus anticoagulant detection dates from 2009 (Pengo et al, J Thromb Haemost 2009), and have been proven to be very useful to reach more uniformity in performance and interpretation of LAC testing. Nevertheless, we feel that for some points these recommendations need another update.

LAC testing in samples from anticoagulated patients, cut-off values, interpretation of results, etc. are some points to reconsider.

Design and methodology (Data expected to collect, sample size and statistical analysis):

To hear the opinion of the broad community of experts in antiphospholipid antibodies, we sent a questionnaire to all SSC aPL members before the SSC meeting in Dublin July 18th 2018.

The results of this questionnaire were presented during this meeting, followed by a panel discussion. For this panel all authors of the 2009 publication who are still active in the field were invited, as well as all current co-chairs of the subcommittee.

For the panel discussion we focused on some selected points, as these had emerged as relevant points to discuss since more variation in opinion was observed in the answers of the questionnaire.

• Timing of LAC testing in relation to a thrombotic event or during pregnancy
• LAC in patients on vitamin K antagonists
• LAC in patients on direct oral anticoagulants
• LAC in patients on heparin
• Methodology: calculation of cut-off value
• Confirmation of a first LAC result

We received 182 responses. The questionnaire results, as well as the outcome of the discussion will be used to review the recommendations on LAC interpretation and measurement.
Questionnaire:

Questionnaire on lupus anticoagulant (LAC) testing: please circle or highlight the appropriate answer(s) to each question in your opinion

1. GENERAL INFORMATION
   i. Are you a:
      A. Laboratory scientist
      B. Haematologist
      C. Rheumatologist
      D. Other specialist clinician, please specify…………………………………..
      E. Other, please specify……………………………………………………….
   
   ii. Type of laboratory you are working in:
      A. Private lab
      B. Hospital lab
      C. University hospital lab
      D. University lab
      E. Other, please specify: ………………………………………………………
      F. Clinician with input into laboratory testing
      G. Clinician without input into laboratory testing
   
   iii. What is the number of LAC tests performed in your lab?
      A. <500/year
      B. 500-1000/year
      C. 1000-2000/year
      D. 2000-4000/year
      E. 4000-6000/year
      F. >6000/year
G. >10 000/year, please specify: ........................................

H. Not applicable

2. PRE-ANALYTICAL FACTORS

i. Timing of LAC testing in relation to a thrombotic event:
   A. No restriction – i.e. test any time after a thrombotic event
   B. Defer testing for at least 12 weeks after a thrombotic event
   C. Defer testing for another time interval after a thrombotic event – please specify………………………………………………………………………….
   D. Depending on the clinical situation: i.e. test immediately if may influence treatment (e.g. CAPS, stroke, MI) and preferably defer testing if VTE
   E. Don’t know or uncertain

ii. Do you think that it is appropriate for LAC testing to be done in patients on vitamin K antagonists (VKAs)?
   A. Yes
   B. No
   C. Don’t know or uncertain

iii. If you have answered ‘Agree’ to question 1. ii above, when do you think it would be appropriate to collect a blood sample for LAC testing in relation to taking a VKA?
   A. Before starting the VKA
   B. At least 7 days after stopping the VKA
   C. Other criteria – please specify ………………………………………………………
      …………………………………………………………………………………………….
   D. Don’t know or uncertain

iv. LAC testing on low molecular weight heparin (LMWH) or unfractionated heparin (UFH) (you may circle more than one option)
   A. LAC testing should not be undertaken in patients on LMWH or UFH
   B. LAC testing is suitable on prophylactic dose LMWH or UFH but not on   therapeutic dose LMWH or UFH
C. In patients on therapeutic dose LMWH, do LAC testing during the trough period, i.e. at least 18 hours after last dose of LMWH

D. In patients on prophylactic dose LMWH, do LAC testing during the trough period, i.e. at least 18 hours after last dose of LMWH

E. Don’t know or uncertain

v. LAC testing in patients on direct oral anticoagulants (DOACs) (you may circle more than one option)

A. LAC testing should not be undertaken in patients on DOACs

B. LAC testing may be undertaken in patients on DOACs during the trough period

C. LAC testing may be undertaken in some circumstances in patients on DOACS during the peak period

D. LAC testing can be performed after prehandling the sample with adsorbant or antidote

Please specify: …………………………………………………………………..
……………………………………………………………………………………..
……………………………………………………………………………………..

E. LAC testing may be undertaken only with adapted method (no aPTT/dRVVT)

F. Don’t know or uncertain

vi. Timing of LAC testing in relation to pregnancy to have representative results (excluding considerations in relation to effect of anticoagulation on LAC detection, which are covered elsewhere in this questionnaire)

A. No restriction, i.e. test any time during pregnancy or postpartum

B. Defer testing until at least 6 weeks after pregnancy

C. Defer testing for another time interval after pregnancy – please specify

……………………………………………………………………………………..

D. Don’t know or uncertain

vii. Blood samples, collected into 0.105 – 0.109 M sodium citrate 9:1, should be double centrifuged at 2000g for 15 min at 15-22°C to achieve a residual platelet count of <109/L

A. Agree

B. Disagree - please state how you think samples should be processed

……………………………………………………………………………………..
……………………………………………………………………………………..

C. Don’t know or uncertain
viii. Plasma for LAC testing should ideally be frozen:
   A. Within 2 hours of collection
   B. Within 2-4 hours of sample collection
   C. Within 4-6 hours of sample collection
   D. Other – please specify……………………………………………………………………...
   E. Don’t know or uncertain

ix. Would you restrict LAC testing if the blood sample is haemolysed?
   A. Yes
   B. No
   If your answer is ‘Yes’, please state the criteria that you use to restrict testing
   ………………………………………………………………………………………………………
   C. Don’t know or uncertain

tax. Would you restrict LAC testing if the sample is lipaemic?
   A. Yes
   B. No
   If your answer is ‘Yes’, please state the criteria that you use to restrict testing
   ………………………………………………………………………………………………………
   C. Don’t know or uncertain

xi. Would you restrict LAC testing if the sample is icteric?
   A. Yes
   B. No
   If your answer is ‘Yes’, please state the criteria that you use to restrict testing
   ………………………………………………………………………………………………………
   C. Don’t know or uncertain
3. TESTING FOR LAC

i. A prothrombin time-International Normalised Ratio (PT-INR), activated partial thromboplastin time (APTT) and thrombin clotting time/Clauss fibrinogen should be performed, to provide background information about unexpected coagulopathies and undocumented anticoagulation.

   A. Agree
   B. Disagree
   C. Don’t know or uncertain

ii. LAC testing should include two phospholipid-dependent clotting tests, based on different principles, with LAC considered positive if one of the two tests gives a positive result.

   A. Agree
   B. Disagree – please specify below what principles you think should be used for LAC testing
   C. Don’t know or uncertain

iii. Which two phospholipid-dependent clotting tests would you do to detect LAC? (circle two options below or F)

   A. A dilute Russell viper venom time test (DRVVT)
   B. APTT using a reagent with proven LA sensitivity
   C. Modified APTT
   D. Dilute prothrombin time
   E. Other – please specify below
   F. Don’t know or uncertain

iv. Should a mixing test for LAC using pooled normal plasma (PNP) be performed?

   A. No
   B. Yes - Patient:PNP ratio = 1:1
   C. Yes - Other ratio of Patient:PNP – please specify below
   D. Don’t know or uncertain
v. Should PNP for a mixing test ideally be:
A. A commercial PNP which has been platelet depleted at collection and is suitable for LAC testing
   B. Prepared in-house
   C. Either commercial or in-house PNP is suitable
C. Don’t know or uncertain

vi. A confirmatory test for LAC should be performed:
A. Only when the screening test is prolonged
B. On all samples being tested for LAC
C. Only when screening and mixing test are prolonged
D. Don’t know or uncertain

vii. Do you think that it is important to perform the components of the LAC tests in a specific order?
A. Yes
B. No
C. Don’t know or uncertain

viii. If your answer to question vii. Above is ‘Yes’, should the order of testing be?
A. Screen, Mix, Confirm
B. Screen, Confirm, Mix
C. All three run at the same time
D. Don’t know or uncertain

ix. An interpretative report should be provided on the LAC result.
   A. Agree
   B. Disagree
4. CUT-OFF VALUES, CALCULATIONS AND QUALITY CONTROL FOR LAC TESTS

i. The plasma used for calculation of normalized ratios should ideally be:
   A. A commercial PNP which has been platelet depleted at collection and is suitable for LAC testing
   B. PNP prepared in-house
   C. Either commercial or in-house PNP is suitable
   D. A commercial LAC negative control plasma
   E. Don’t know or uncertain

ii. If in-house pooled PNP is used for the calculation of normalized ratios, this should be prepared from:
   A. At least 6 healthy adult donors
   B. At least 40 healthy adult donors
   C. A larger number of adult donors – please specify the number you think is appropriate…

iii. Normalization of clotting times should be derived using:
   A. Denominator = pooled normal plasma analysed in the same run
   B. Denominator = mean of reference interval
   C. Other – please specify ………………………………………………………………………
   D. Don’t know or uncertain

iv. The cut-off for screen, mixing and confirmation tests based on testing on plasmas from healthy donors should be:
   A. The value above the 99th centile of the distribution
   B. The value above the 97.5th centile of the distribution
   C. Other – please specify……………………………………………………………………
   D. Don’t know or uncertain

v. The manufacturer cut-off values for LA positivity should be locally validated.
vi. Do you calculate your in-house cut-off values?
A. Yes
B. No
C. If no: please specify why……………………………………………………………………

vii. In-house cut-off values (percentiles) should be calculated on how many plasmas from healthy donors?
A. <20
B. 20-60
C. 60-120
D. >120
E. Other, please specify……………………………………………………………………
F. Don’t know or uncertain

viii. The cut-off for the percentage correction (if used) based on testing on plasmas from healthy donors mixed with the PNP at 1:1 proportion should be:
A. The value above the 99th percentile of the distribution
B. The value above the 97.5th percentile of the distribution
C. Other – please specify……………………………………………………………………

ix. How do you interpret the mixing test:
A. Rosner index (index of circulating anticoagulant)
B. Normalized clotting time
C. Both Rosner index and normalized clotting time
5. LAC TESTING IN PATIENTS ON ANTICOAGULANT

i. If doing LAC testing in patients on VKAs

A. If INR <1.5, test for LAC on undiluted plasma
B. If INR 1.5 - <3.0, use a 1:1 dilution of patient plasma and PNP in both screen and confirm parts of the DRVVT
C. If INR 1.5 - <3.0, use a 1:1 dilution of patient plasma and PNP in both screen and confirm parts of the SCT/aPTT
D. Screen and confirm tests on 1:1 mixture with PNP regardless of INR (unless excessively raised, >8.0)
E. Different criteria to those in A-D, please specify

F. Taipan Venom time test/Ecarin clotting time (TSVT/ECT) ratio
G. DRVVT on 1:1 mixture with PNP as well as TSVT/ECT
H. Don’t know or uncertain

ii. If doing LAC testing in patients on LMWH or UFH the plasma level of heparin should be verified, to ensure that the LAC method will be unaffected by anticoagulation, by: (you may choose more than one of the options below)

A. Anti-Xa assay for LMWH if patient on therapeutic but not on prophylactic dose LMWH
B. Anti-Xa assay for LMWH regardless of whether patient on therapeutic or prophylactic dose
C. APTT Ratio or anti-Xa assay for UFH if patient on therapeutic, but not on
prophylactic dose UFH

D. APTT Ratio or anti-Xa assay for UFH if patient on UFH regardless of whether patient on therapeutic or prophylactic dose

E. Don’t know or uncertain

iii. If doing LAC testing in patients on DOACs: (you may choose more than one of the options below)

A. For patients on direct factor Xa inhibitors, undertake LAC testing during trough period using DRVVT together with assay for specific DOAC

B. For patients on factor Xa inhibitors, TSVT/ECT ratio is suitable

C. State what test you would do for LAC testing in patients on dabigatran

D. Don’t know or uncertain

6. COMMENTS – Please detail below any comments about LAC testing, either about the points covered above or any further issues.

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Please fill in your email address .................................................................

Results of the questionnaire

See attachment
SSC Subcommittee Project/Collaborative Project

Expected timeline:

- Project stage/set up: 2018
- Launch: SSC meeting 2018
- Duration: 2018-2020
- Finalization/analysis: 2020
- Reporting: 2019-2020

Expected outcomes (ie. publications):

- Report of the questionnaire
- Guidance/guideline document on LAC interpretation

Description of project set/up and management, needed infrastructure and resources (summary):

The SSC Executive office was very helpful in set-up of the questionnaire and sending it to the SSC members, as well as in generating a report (RedCap).

Possible references: