Do Guidelines for Lupus Anticoagulant Testing Work in Practice?

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Topics for Discussion

Terminology

Acronym	Definition
BCSH	British Committee for Standards in Haematology
CAP	College of American Pathologists
CLSI	Clinical and Laboratory Standards Institute
ECAT	External quality Control of diagnostic Assays and Tests
EQA	External Quality Assessment
ISTH	International Society on Thrombosis and Haemostasis
NASCOLA	North American Specialized Coagulation Laboratory Association
SSC	Scientific and Standardization Committee (of the ISTH)
UK NEQAS	United Kingdom National External Quality Assessment Scheme

Guidelines:

A Historical Perspective

ISTH SSC Guidelines

- **1983**: Report of the Working Party on Acquired Inhibitors of Coagulation: studies of the "lupus" anticoagulant. (Green, et al. Thromb Haemost 49:144–6)
- **1991**: Guidelines for testing and revised criteria for lupus anticoagulants. SSC Subcommittee for the Standardization of Lupus Anticoagulants. (Exner, et al. Thromb Haemost 65:320–2.)
- **1995**: Criteria for the diagnosis of lupus anticoagulants: an update. On behalf of The Subcommittee on Lupus Anticoagulant/Antiphospholipid Antibody of the Scientific and Standardisation Committee of the ISTH. (Brandt, et al. Thromb Haemost 74:1185-90.)
- **2009**: Update of the guidelines for lupus anticoagulant detection. (Pengo, et al. J Thromb Haemost 7:1737-40.)

Other Guidelines

- **British - 2000**
  - Guidelines on the investigation and management of the antiphospholipid syndrome. (Greaves, et al. Br J Haematol 109:704-15.)
  - Reiterated ISTH SSC 1995 guidelines but discussed pre-analytical issues and the need for establishing local reference intervals
  - Perform immunoassays for anticardiolipin (aCL)/β_2-Glycoprotein I (β_2-GPI)
- **USA - 2002**
  - Antiphospholipid antibodies (CAP consensus conference). (Triplett. Arch Pathol Lab Med 126:1424-9.)
  - Reiterated ISTH SSC 1995 guidelines
- Antiphospholipid Syndrome (APS) classification
  - **1999**: Wilson WA, et al. International consensus statement on preliminary classification criteria for definite antiphospholipid syndrome. Arthritis Rheum 42:1309-11.
  - **2006**: Miyakis S, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). J Thromb Haemost 4:295-306.

Recommendations from 1995 SSC

- Nine recommendations were offered in the 1995 SSC report on LA
  - Four of these contained the diagnostic criteria first outlined in 1991 but with additional clarification
  - One recommendation (#9) concerned nomenclature (retention of term "lupus anticoagulant")
- Remaining recommendations dealt with:
  - Platelet count platelet poor plasma (< 10 x 10^9/L) [Recommendation #1]
  - Confirmatory assays [Recommendation #5]
    - Use same assay principle as screening test that was initially found to be abnormal
  - Performance of routine clotting tests, such as PT and APTT [Recommendation #6]
    - Use to evaluate possibility of other coagulation disorders that may interfere with LA methodology
    - If chosen method for screening or confirmation is known to be sensitive to heparin, a Thrombin Time may be helpful in detecting its presence
  - Solid phase assays for antiphospholipid antibodies (aPL) should not be considered as confirmatory procedures for LA activity [Recommend. #7]

Criteria for Diagnosis of LA –1991, 1995, 2009

Brandt JT. Thromb Haemost 1995;74:1185-90

1. Prolongation of at least one "in vitro" phospholipid-dependent clotting test (Screening Test) [Recommendation #2]
   - Recommendation #2: *Two or more tests should be used to screen for LA and these should represent different assay principles*
2. Evidence of inhibitory activity shown by the effect of patient plasma on pooled normal plasma (Mixing Test) [Recommendation #3]
3. Evidence that the inhibitory activity is dependent on phospholipid (Confirmatory Test) [Recommendation #4]. *This may be achieved by addition or alteration of phospholipid, hexagonal phase phospholipid, or platelets in the test system.*
4. LA must be carefully distinguished from other coagulopathies that may give similar laboratory results or may coexist with LA [Recommendation #6]
   - Recommendation #8: *Specific factor assays and the clinical history may be helpful in differentiating LA from these other possibilities*

2009 SSC Guideline Update

Pengo V. J Thromb Haemost 2009;7:1737-40.

- Patient selection
  - Goal is to minimize inappropriate requests for LA testing
  - Testing should be limited to:
    - Patients who have a significant probability of having APS
    - Patients who have an unexplained prolonged APTT discovered during routine testing
- Recommendations for optimal laboratory detection of LA
  - Specimen procurement and sample processing
  - Issues related to testing
    - Screening – two tests of different principles [LA-sensitive APTT & dRVVT recommended]
    - Mixing test
    - Confirmatory test
- Expression of results (normalized ratios)
- Interpretation of test results
  - Use locally derived cut-off values
  - Consider interferences such as vitamin K antagonists or heparin
- Reporting of results
  - Link LA testing with other aPL testing such as aCL and aβ_2-GPI

CLSI H60 LA Testing Guideline

- Timeline
  - April 2009: Proposal submitted (preliminary approval October 2009)
  - January 2010: Call for subcommittee member nominations
    - 28 members from 7 countries representing academia, reference & hospital laboratories, EQA programs, industry, and government
      - Includes SSC guideline authors: Exner (1991), Brandt (1995), de Groot (2009)
  - March 2010: Final project approval
  - May and July 2010: Conference calls
  - October 2010: First face-to-face meeting to review first draft of document
- Goal
  - Continue to build upon previous global initiatives and also harmonize with and add clarity to current guidelines
  - Present information in a succinct, practical, and easy to understand format

Scope of CLSI H60 Guideline

- Provide recommendations for performance and interpretation of screening assays, mixing tests, and confirmatory assays
  - Address pre-examination issues, examination concerns, and post-examination matters that pertain to interpretation of individual tests or combinations of assays
- The intended users are laboratory personnel responsible for performing LA testing, physicians (hematologists, pathologists, rheumatologists), EQA programs, and manufacturers of reagents used in LA testing
- Two methodologies are used for the diagnosis of APS however the guideline is limited to clot-based coagulation assays used as surrogates for identifying LA
  - Guideline will not address solid-phase testing for antiphospholipid antibodies (anti-cardiolipin or anti-β_2-Glycoprotein I) because detection of these specific antibodies may or may not relate to the laboratory anomaly of a prolonged APTT

Addressing Laboratory Compliance with LA Guidelines

Methods for Assessing Compliance

- Indirect via EQA surveys
  - Samples "known" to be LA positive (strong or weak) or normal are distributed by EQA programs worldwide
  - Data derived from surveys informs as to which assays are performed, reagents/instruments used, and if appropriate conclusions are reached (agreement with "known")
- Direct assessment
  - Questionnaires that ask laboratories to outline their testing schemes for identifying a LA
    - Conformity can be assessed by direct comparison of responses to guideline criteria
  - Retrospectively analyze EQA data to ascertain guideline conformity relative to test data

Indirect EQA Published Studies

- Using LA positive or LA negative lyophilized samples
  - Exner (T&H 1990 [ISLA-1]), Brandt (APLM 1991), Roussi (AJCP 1996), Jennings (T&H 1997), Goudemand (T&H 1997), Jacobsen (T&H 2000 [ISLA-5]), Favaloro (STH 2005), Favaloro (T&H 2006)
- Using normal plasma spiked with monoclonal antibodies
  - Arnout (T&H 1999 [ECAT]), Jennings (JTH 2004 [NEQAS])
- Using a sample containing affinity-purified IgG from LA positive patient
  - Tripodi (Clin Chem 2003)
- Referral of locally indentified LA positive samples to a reference laboratory
  - Pengo (JTH 2007)

Direct Assessment of Compliance

- EQA LA positive or LA negative lyophilized samples
  - UK NEQAS
    - Jennings I, Greaves M, Mackie IJ, Kitchen S, Woods TA, Preston FE. Lupus anticoagulant testing: improvements in performance in a UK NEQAS proficiency testing exercise after dissemination of national guidelines on laboratory methods. Br J Haematol 2002;119:364-9
  - NASCOLA
    - Dembitzer FR, Ledford-Kraemer MR, Meijer, P, Peerschke EIB. Lupus anticoagulant testing; performance and practices by North American Clinical Laboratories. Am J Clin Pathol 2010;134:764-73.
- Questionnaire
  - NASCOLA and ECAT
    - Moffat KA, Ledford-Kraemer MR, Plumhoff EA, McKay H, Nichols WL, Meijer P, Hayward CP. Are laboratories following published recommendations for lupus anticoagulant testing? An international evaluation of practices. Thromb Haemost 2009;101:178-84.

UK-NEQAS Interpretations

	LA positive plasma		LA negative plasma	
Overall interpretations:	n	%	n	%
Negative	43	18.5	227	97.5
Borderline/Equivocal	28	12.1	3	1.3
Weak positive	71	30.6	1	0.4
Moderate positive	75	31.9	2	0.8
Strong positive	16	6.9	0	0.0

Jennings. Br J Haematol 2002;119:364-9.

UK-NEQAS Compliance - BCSH Guidelines

LA Positive Sample

Overall interpretations:	Compliant (n = 147) %	Non-compliant (n = 85) %
Negative	13	32
Borderline/Equivocal	14	8
Weak positive	31	31
Moderate positive	34	27
Strong positive	8	2

Jennings. Br J Haematol 2002;119:364-9.

Are Laboratories Following Published Recommendations for LA Testing?

An International Evaluation of Practices

Results from two NASCOLA/ECAT Questionnaires

Moffat K. Thromb Haemost 2009;101:178-84.

Study Goals and Methods

- Goals
  - Determine LA test practices used by laboratories
  - Determine if laboratory practices conformed to published recommendations (1995 ISTH-SSC, BCSH, CAP)
- Methods
  - Two patterns of practice questionnaires distributed
  - Q1 2005 (113 laboratories)
    - NASCOLA (46 of 48 laboratories responded [96%])
    - ECAT (67 of 150 laboratories responded [45%])
  - Q2 2007 (96 laboratories responded – 85 completed)
    - NASCOLA (43) and ECAT (42)

Focus of Q1 and Q2

- Q1 addressed issues relating to:
  - Screening assays
  - Mixing studies
  - Confirmatory assays
  - Interpretations
  - Antiphospholipid assays
  - Testing algorithms (requested laboratories submit their LA testing algorithms of which 104/113 were received)
- Q2 was formatted to ascertain if LA testing practice patterns aligned with specific ISTH recommendations
  - Responses from Q1 gave rise to Q2
    - Expanded upon or clarified issues raised in Q1

Screening Assays - Responses Q1 & Q2

Test	NASCOLA		ECAT	
(Multiple Responses)	Q1	Q2	Q1	Q2
LA sensitive APTT*	NA	88%	NA	94%
dAPTT*	NA	5%	NA	10%
dRVTT	91%	98%	85%	90%
dPT	24%	21%	25%	50%
KCT	13%	7%	26%	47%

Legend: APTT, Activated Partial Thromboplastin Time; dAPTT, dilute APTT; dRVVT, dilute Russell's Viper Venom Time; dPT, dilute Prothrombin Time; KCT, Kaolin Clotting Time; *Potential overlap between categories; NA, Not applicable as participants were not asked specifically to identify sensitivity of APTT reagent

- **2009 SSC Guidelines recommend using LA-sensitive APTT and dRVVT**

Mixing Studies - Responses Q1

- Data from LA algorithm analysis showed that some laboratories do not comply with ISTH criterion for mixing studies
  - 25-35% *do not* perform APTT mixing studies
  - 45-55% *do not* perform dRVVT mixing studies
- ISTH criterion requires that pooled normal plasma be used for mixing studies
  - 77% of NASCOLA laboratories use a commercial source
  - Only 11% of ECAT laboratories use a commercial source
    - Number may not be accurate as 40% of ECAT laboratories failed to identify their source for NPP
  - 1995 guidelines were not followed by 8% of laboratories
    - Used commercial, *lyophilized control* plasmas
      - ***Lyophilized plasmas now permitted in 2009 SSC Guidelines***

Criteria for Abnormal 1:1 Mixing Study (Q1)

	Routine APTT reagent (74% Respondents)		LA-Sensitive APTT reagent (54% Respondents)	
	NASCOLA	**ECAT**	**NASCOLA**	**ECAT**
Failure to correct to within +2 SD	71%	61%	62%	74%
Failure to correct to within +3 SD ***Now recommended in 2009 SSC Guidelines***	6%	15%	62%	0%
Failure to correct to within 5 seconds of NPP	47%	36%	50%	32%
Failure to correct to within 10% of NPP	17%	16%	14%	18%
ICA (Rosner) of >15 ***Now recommended in 2009 SSC Guidelines***	6%	50%	17%	53%

Legend: NPP, Normal Pooled Plasma; ICA, Index of Circulating Anticoagulant

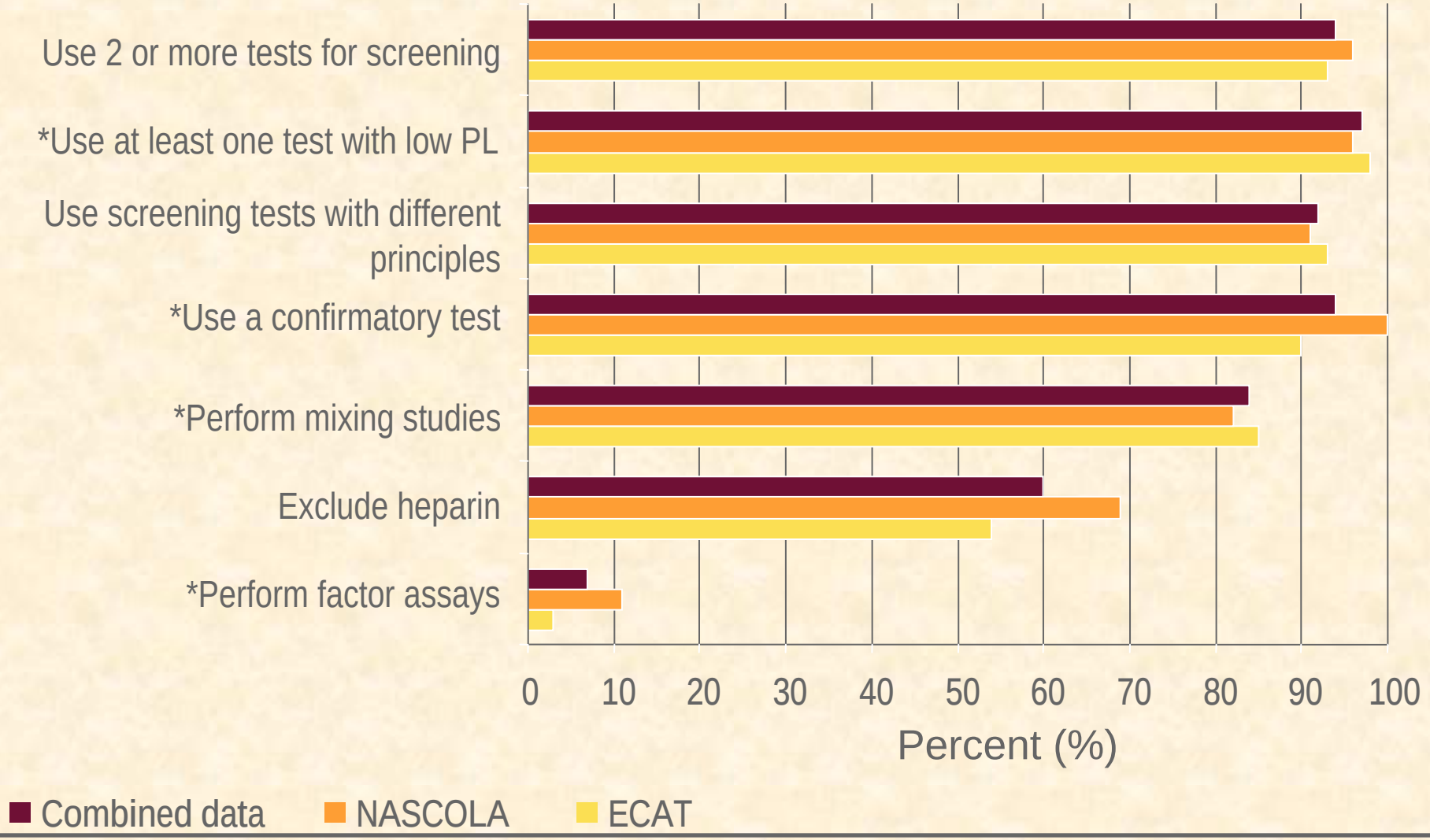
Confirmatory Assays - Responses Q1

- 97% of laboratories that perform a dRVVT screening assay also do a dRVVT confirm assay
  - 79% do not perform the confirm assay if the dRVVT screen is normal
- Laboratories that perform both dRVVT assays use a Screen/Confirm ratio for result reporting
  - NASCOLA = 62% ECAT = 43%
- Other altered/high/ phospholipid assays
  - Hexagonal phospholipid neutralization test
    - Performed by 40% (n=45/112) of laboratories
      - NASCOLA: 70% (n=32/46)
      - ECAT: 20% (n=13/66)
  - Platelet Neutralization Procedure
    - Performed by 31% (n=35/113) of laboratories
      - NASCOLA: 48% (n=22/46)
      - ECAT: 19% (n=13/67)

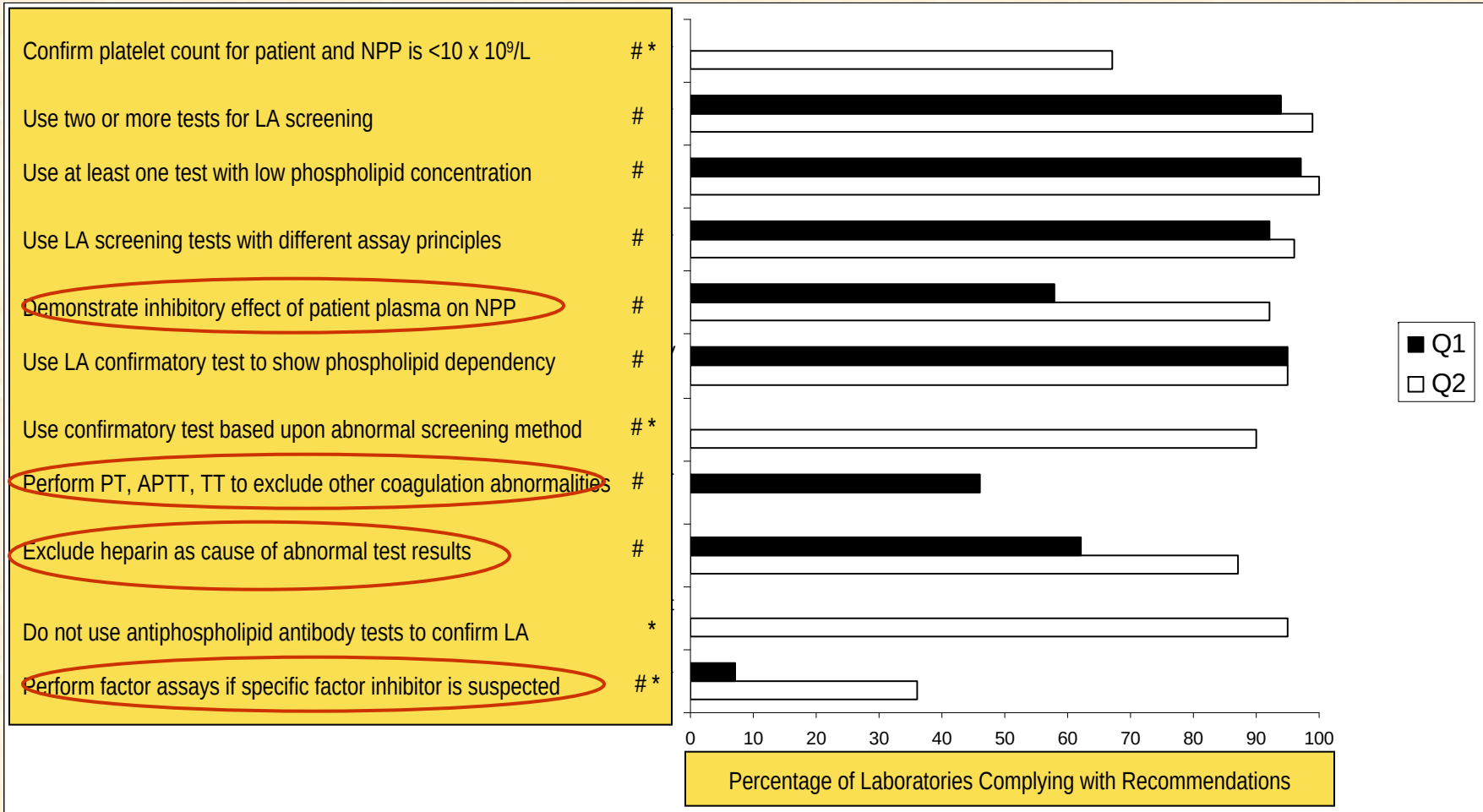
Interpretation - Responses Q1

- 69% of laboratories have a set panel (algorithm) of LA tests
  - Among this group:
    - 53% allow tests to be ordered separately
    - 70% include tests for aPL in their panel
- 89% offer interpretation of raw data from compiled LA tests
  - ***Now recommended in 2009 SSC Guidelines***
  - For a positive LA interpretation, 44% of these laboratories grade the strength of the inhibitor (degree of positivity)
    - Equivocal, weakly positive, moderately positive, strongly positive
  - Individual performing interpretation (multiple responses)
    - Bench technologist (39%)
    - Supervisor (49%)
    - Medical director (81%)
    - Other clinician (30%)

Analysis of 104/115 LA Testing Algorithms (Q1) as to conformity with 1995 ISTH Criteria* & Recommendations



Summary of NASCOLA and ECAT Participant Compliance with ISTH & BCSH Guidelines for Q1 and Q2



 # Recommendations found in both ISTH & BCSH guidelines; * Information assessed only in Q2

Conclusions Q1 & Q2

- Q1 showed that, in contrast to the 1995 ISTH SSC criteria / recommendations for LA testing, the testing practices of a significant proportion of NASCOLA & ECAT laboratories do not comply with:
  - Criterion #2
    - 8% fail to use NPP for mixing studies
    - 41% fail to perform a mixing study for a dRVVT screening test
  - Criterion #4
    - 93% fail to perform factor assays to differentiate LA from other coagulopathies
  - Recommendation #6
    - 40% do not evaluate for heparin if the APTT is prolonged
- Q2 showed that testing practices comply with recommendations to:
  - Use platelet poor plasma with $<10 \times 10^9$platelets/L (67%)
  - Use two or more screening tests (96%) representing different assay principles (94%)
  - Use same test method, giving an abnormal LA screen, to confirm LA phospholipid dependency (90%)
  - Not to use solid phase phospholipid antibody testing to confirm LA (95%)
- Q2 showed noncompliance (~65%) with criterion #4: to perform factor assays in order to differentiate LA from specific factor inhibitors

Lupus Anticoagulant Testing

Performance and Practices by North American Clinical Laboratories

Dembitzer FR. Am J Clin Pathol 2010;134:764-73.

Study Goals and Methods

- Goals
  - Evaluate LA testing practices by North American clinical laboratories
  - Assess compliance with ISTH SSC 1995 guidelines relating to number and types of screening tests, mixing tests, and confirmatory tests that are performed
  - Assess impact of compliance with guideline on accuracy of overall result interpretation
- Methods
  - Data from a total of 248 testing panels were analyzed from 5 consecutive EQA challenges (46-53 participants/survey)
  - EQA samples consisted of high, intermediate (2), and low positive LA as well as a normal
  - Laboratories analyzed samples according to their local testing practices

Compliance Rates with "Weak" LA

	2008-2	2008-3	2008-4
	Intermediate Titer LA	Low Titer LA	Intermediate Titer LA (Diluted)
Final Interpretation (n)	50	53	50
Positive*	27	35	34
Negative	14	13	12
Borderline	9	5	4
Non-Compliance [n (%)]	10 (20%)	20 (38%)	11 (22%)
No Mix (n)	5	13	6
No Mix/Confirm (n)	2	5	1
Insufficient Testing (n)	3	2	4
Misdiagnosis** (%)			
All Laboratories	14 / 50 = 28%	13 / 53 = 25%	12 / 50 = 24%
Compliant Laboratories	[77%] 11 /50-10 = 27%	[46%] 6 / 53-20 = 18%	[67%] 8 / 50-11 = 20%
Non-Compliant Laboratories	[23%] 3 / 10 = 30%	[54%] 7 / 20 = 35%	[33%] 4 / 11 = 36%
# of Tests Performed (mean + SD)			
Positive Result	6.1±1.8	6.3±1.8	6.3±1.7
Negative Result	6.3±1.3	4.8±1.3	5.8±1.1
Borderline Result	7.1±1.6	5.3±1.0	5.7±0.6

Legend: * includes the following interpretations: CP=clearly positive, P=positive; PP=probably positive; ** False Negative Results

Calculations for Compliant Laboratories: number of laboratories [based on %] that made misdiagnosis / (total number of laboratories – those laboratories that were non-compliant)

Calculations for Non-Compliant Laboratories: number of laboratories [based on %] that made misdiagnosis / number of laboratories that were non-compliant

Summary of Practices Study

- Rates for non-compliant events were 8 - 38%
  - Highest degree of non-compliance was with criterion #2
    - Majority failed to perform a Screen Mixing Test and some failed to perform a Confirm Mixing Test
      - Findings consistent with results from NASCOLA/ECAT Q1 questionnaire
  - Lack of compliance also seen with number of assays performed (insufficient numbers)
    - Had no impact on LA identification (correctness or lack thereof)
- With the exception of one laboratory, those which were non-compliant were so inconsistently
  - May reflect perceptions as to type of testing warranted when challenged with intermediate to weak LA
- Intermediate to weak LA were misdiagnosed by ~25% of laboratories
  - Rates comparable to those reported by UK-NEQAS (18.5%: see slide 17)
- Compliance and outcomes
  - **18 - 27% false negative rates** for **compliant** laboratories
    - UK-NEQAS rates similar at 13% false negative rate if compliant (see slide 18)
  - **30 - 36% false negative rates** for **non-compliant** laboratories
    - UK-NEQAS rates similar at 32% if non-compliant (see slide 18)

Concluding Remarks and Future Directions

Concluding Remarks

- Goal of a guideline is to standardize an approach to LA testing with the hopes that recommendations gain acceptance and by that improve testing quality
- Reasons for non-compliance are multifactorial
  - "*Purist*" approach in writing a guideline in contrast to *practical* issues faced in the laboratory or to regional *practices* (North America *v* Europe)
  - Financial constraints, availability of assays
  - Physician ordering practices
  - Marketplace driven (popularity of certain assays)
  - Misinterpretation or misunderstanding of recommendations

Future Directions

- Challenges abound!!
- **Laboratories** could design relatively straightforward experiments concerning almost every aspect of LA testing
  - Study in which one laboratory tests a number of patient samples having a weak LA with a variety of reagents from various manufacturers to provide insight as to assay robustness
- **EQA programs** worldwide can help answer a core question: is compliance with guidelines necessary for making a correct diagnosis of LA?
  - Specifically linking criteria with testing and interpretive outcomes
- **Clinicians** need to apply an evidence-based approach to the significance of weak LA
- **Researchers/Manufacturers** should be challenged to find better LA assays than the surrogates that are currently available

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