ICSH REVIEW
OF NEW ESR TECHNOLOGY

THE ICSH WORKING GROUP FOR ESR STANDARDIZATION:

Richard McCafferty, Dublin, Ireland
Gini Bourner, Guelph, Canada
Professor Young Kyung Lee, Hallym, Korea
Professor Mingting Peng, Beijing, China
Professor Mario Plebani, Padova, Italy
Alexander Kratz, New York, USA; Chair
A VERY BRIEF HISTORY OF THE ESR

- ESR was first described in 1894 by Dr. Biernacki, as well as independently thereafter by Drs. Hirszfeld, Fahraeus and Westergren.
- Principle: Sedimentation of red cells in plasma provides a measure of the level of acute-phase proteins and therefore inflammation.
- ESR remains a widely used test for the screening and monitoring of diseases that affect plasma proteins.
- Second most-often ordered test in Hematology (after FBC/CBC).
- Rapid proliferation of new methods that claim to report the same results as the Westergren method.

ICSH AND THE ESR

• The first International Council for Standardization in Hematology ESR panel was established in 1965 and included Dr. Westergren. The decription of the reference method was published in 1973.

• The ICSH has issued standards for the ESR in:
  – 1973
  – 1977
  – 1988
  – 1993
  – 2011
The reference method for the measurement of the ESR should be based on the Westergren method, which is a specific test for ESR, with modifications.

The reference method should use either whole blood anticoagulated with EDTA and later diluted with sodium citrate or saline (4:1) or whole blood anticoagulated with sodium citrate (4:1) in Westergren pipettes.

The ESR pipettes can be made of glass or plastic (with specific characteristics). They must be colorless, with a minimum sedimentation scale of 200 mm, a minimum bore of 2.55 mm, which should be constant within 5%.
A protocol for the evaluation of alternative technologies against the reference method was outlined:

- The new technologies must be tested over a range of ESR values of 2-120 mm.
- In this comparison, 95% of the differences should be 5 mm or less, with larger differences associated with higher ESR values.
- A minimum of 40 samples should be tested in 3 different groups of values: 1-20, 21-60, and more than 60 mm.
- The statistical methods recommended for ESR evaluations are the coefficient of correlation, the Passing-Bablock regression, and the Bland-Altman statistical method.
HERE IS WHAT YOU MAY BE THINKING NOW:
THE ESR GUIDELINES SEEM TO COVER EVERYTHING VERY WELL; WHY DO WE NEED NEW GUIDELINES? WHAT HAS CHANGED???
NEW INSTRUMENTS APPROVED BY THE FDA FOR THE US MARKET SINCE 2011:

- Test 1
- Roller LC
- Roller PN
- AirScan ESR STAT PLUS
- Excyte M Automated ESR Analyzer
- Excyte 40 Automated ESR Analyzer
- Excyte 20 Automated ESR Analyzer
- Excyte 10 Automated ESR Analyzer
- Excyte Mini Automated ESR Analyzer
- iSED Automated ESR Analyzer

Source: Federal Drug Administration (FDA)
### REASONS FOR USE OF NEW ESR INSTRUMENTS

<table>
<thead>
<tr>
<th>Reason</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduced exposure of laboratory personnel to infections agents</td>
<td></td>
</tr>
<tr>
<td>Ability to use standard EDTA tubes</td>
<td></td>
</tr>
<tr>
<td>Reduction of analysis time from one hour to seconds</td>
<td></td>
</tr>
<tr>
<td>Reduction of probability of human error</td>
<td></td>
</tr>
<tr>
<td>Reduction in the amount of labor needed, leading to increased economic efficiency</td>
<td></td>
</tr>
<tr>
<td>Ability to interface instrumentation to the EMR, reducing transcription errors and allowing instantaneous communication of results to clinical staff.</td>
<td></td>
</tr>
</tbody>
</table>
WHY REVIEW THE ICSH GUIDELINES FOR THE ESR NOW?

• New instruments on the market
  – This leads to potential new issues with
    • Technical validation
    • Clinical interpretation of data
    • QC and Proficiency Testing

• Reports in the literature indicate that different methods differ in susceptibility to interferences; this may need to be addressed in new guidelines.
WHY REVIEW THE ICSH GUIDELINES FOR THE ESR NOW?

• The present ESR guidelines correctly identify the Westergren method as the reference method, and state that any new method must be correlated to the Westergren method.

• However, they do not address what to do if a non-Westergren method does not correlate to the Westergren method.
TECHNICAL ISSUES TO BE REVIEWED

- Validation Studies, to assess factors that can affect results:
  - Interferences
    - Lipemia
    - Hemolysis
    - Paraproteins
  - Patient’s age
  - Hematocrit
  - Stability Studies
  - Precision Studies
IN SUMMARY:

- Multiple new ESR instruments have come on the market since 2011.
- In order to continue to offer up-to-date performance guidelines for the second-most frequently ordered test in hematology, a review of present guidelines as they apply to non-Westergren methods is indicated.
IMPLEMENTATION PLAN

• Assembly of an international team of five to seven experts.
• Assignment of specific areas of primary responsibility to each member of the working group
• Phone conferences and e-mail exchanges over approximately one year, with circulation of draft documents (partial and later complete) via e-mail.
• Total duration of project: 12 to 18 months.
• Estimated time of publication: Early 2017.
PROJECT PLAN

• Aim of the paper
• Background
• Methods
• Results
• Discussion and Conclusions
INTRODUCTION

• **Aim of the paper:**
  – To produce an updated ICSH guideline for standardization of the ESR

• **Background:**
  – History of ESR
  – Clinical uses of ESR
  – Overview of previously published guidelines for the ESR (CLSI, ICSH)
METHODS

• Obtain lists of:
  – Manufacturers of ESR analyzers
  – Methods for ESR analysis
• Literature review of evidence-based reports of ESR methods
• Review of EQA data of performance of different methods
RESULTS

• Lists of manufacturers of ESR analyzers and their methods
• Findings of the completed literature review
• Summary of the EQA data
PROGRESS SO FAR
(November 2015-April 2016)

• December 7, 2015: Working group membership finalized
• February 3, 2016: Action plan in place, all working group members have received their assignments.
• February 28, 2016: First EQA data shared with group
• April 20, 2016: 6/6 sets of EQA data are submitted
• April 26, 2016: Overview of the Past ESR Guidelines is submitted
• April 28, 2016: Literature Review is submitted
• May 5, 2016: Additional EQA data are submitted
SUMMARY
OF PROGRESS SO FAR
(November 2015 - May 2016)

We have completed so far:
- Collection of EQA data
- Literature Review
- A draft outline of the paper, with a very advanced draft of the Overview of Past ESR Guidelines
THE EQA DATA SO FAR

- **USA and Canada (CAP):** approximately 4,000 laboratories:
  - Have different survey material for Westergren and each of three non-Westergren principle of measurement.

- **Australia:** 493 laboratories:
  - Have separate modules for Westergren and non-Westergren methods

- **China:** 729 laboratories:
  - Two third of laboratories use automated methods

- **Korea:** 496 laboratories:
  - No EQA program for ESR
THE EQA DATA SO FAR

- **Italy:** 102 laboratories:
  - Separate EQA material for Westergren and non-Westergren methods
- **United Kingdom:** 362 laboratories: 3 pilot surveys
  - Methodologies grouped for data analysis, despite all methods claiming traceability back to Westergren, as there was a difference in results, most noticeable at higher ESR values.
- **Ireland:** 57 laboratories:
  - Half of the laboratories use automated methods
<table>
<thead>
<tr>
<th>Instrument</th>
<th>Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>StaRRsed</td>
<td>Westergren</td>
</tr>
<tr>
<td>Sedisystem</td>
<td>Westergren</td>
</tr>
<tr>
<td>Test 1</td>
<td>Photometric Rheology</td>
</tr>
<tr>
<td>Vesmatic</td>
<td>Modified Westergren</td>
</tr>
<tr>
<td>ESR STAT PLUS</td>
<td>Centrifugation</td>
</tr>
<tr>
<td>iSED</td>
<td>Photometric Rheology</td>
</tr>
<tr>
<td>Excyte</td>
<td>Measurement of sedimentation at 30 minutes, mathematically adjusted to a result that is comparable to a 1 hour Westergren ESR</td>
</tr>
<tr>
<td>Streck ESR-Auto Plus</td>
<td>Measurement of sedimentation at 30 minutes, mathematically adjusted to a result that is comparable to a 1 hour Westergren ESR</td>
</tr>
</tbody>
</table>
EQA FINDINGS SO FAR

- Data from over 6000 laboratories from four continents and 7 countries: Australia, Canada, China, Ireland, Italy, Korea, UK, and USA
- Non-Westergren methods are the majority
- Correlations between the non-Westergren methods and Westergren to non-Westergren show significant variations
- Many EQA organizations have separate survey material for non-Westergren and Westergren methods.
LITERATURE REVIEW

• Papers from: Finland, Netherlands, Korea, Italy, Turkey, France, USA, Croatia.
• Data on:
  • Method Correlations
  • Interferences
  • Clinical applications, e.g. disease diagnosis, prognosis
  • Reference Ranges
• Analysis ongoing
NEXT STEPS

• Review of EQA data and Literature Review by all working group members
• Composition of a draft manuscript
• Discussion and editing of the draft manuscript
POSSIBLE DISCUSSION AND CONCLUSIONS

• Guidelines for clinical users to choose an ESR method
• Manufacturer obligations, e.g.
  – Non-Westergren methods should be clearly marked as such
  – Determine correlation with Westergren method (accuracy)
  – Determine precision
  – Determine age-specific reference ranges
  – List all interferences tested for, with results
POSSIBLE DISCUSSION AND CONCLUSIONS, continued

• User obligations, e.g.
  – Validation studies to determine suitability of a new non-Westergren method for the laboratory and its patient and clinician population
  – Validate manufacturer’s reference ranges
ICSHE REVIEW
OF NEW ESR TECHNOLOGY

ACKNOWLEDGEMENTS

THE PROJECT GROUP:
Richard McCafferty, Dublin, Ireland
Gini Bourner, Guelph, Canada
Professor Young Kyung Lee, Hallym, Korea
Professor Mingting Peng, Beijing, China
Professor Mario Plebani, Padova, Italy
Alexander Kratz, New York, USA; Chair
ACKNOWLEDGEMENTS

THE PROJECT GROUP would also like to thank all those who provided EQA data including CAP, CRB (Padova Italy), LabQuality (Finland), IEQAS (Ireland), UK NEQAS
ICSH REVIEW
OF NEW ESR TECHNOLOGY

THANK YOU FOR YOUR ATTENTION!