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ICSH review of the measurement of the erythocyte sedimentation rate

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SUMMARY

In recognition of the need for a standardization of the measurement of the erythrocyte sedimentation rate (ESR), the International Council for Standardization in Haematology makes the following recommendations: (i) The reference method for measurement of the ESR should be based on the Westergren method, which is a specific test for the ESR, with modifications, (ii) The reference method for measurement of the ESR 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, (iii) The ESR pipettes can be of glass or plastic (with specific characteristics). It must be colourless; 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 methodologies against the reference method is 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. This reference method replaces all earlier standardized and reference methods.

INTRODUCTION

The method for the erythrocyte sedimentation rate (ESR) was first described in 1921 by Dr R Fahraeus and Dr A Westergren (Fahraeus, 1921; Westergren, 1921), and it rapidly became a common screening test worldwide for acute phase proteins and chronic diseases (Westergren, 1926). Despite its limitations and the introduction of other more specific markers of inflammation, the ESR remains a widely used test for the screening and monitoring of infectious, autoimmune, malignant and other disease processes that affect plasma proteins and the sedimentation rate. From the outset, the ESR was a complex and poorly understood test, and there is no method that can ensure that the test is not influenced in misleading ways by variations in relative erythrocyte volume (i.e. haematocrit and red cell shape and size) and by other unidentified confounding factors.

The first expert International Council for Standardization in Haematology (ICSH) ESR panel was established in 1965 and included Dr A Westergren as a foundation member; the description of the reference method was published in 1973 (ICSH, 1973). Further revisions of the reference method by the ICSH have been published (ICSH, 1977, 1988, 1993), and the present document designates these earlier guidelines as ICSH-1973 (ICSH, 1973), ICSH-1977 (ICSH, 1977), ICSH-1988 (ICSH, 1988) and ICSH-1993 (ICSH, 1993).

Since 1991, many evaluations of new ESR analysers using alternative methods have been published. However, most evaluations failed to calibrate their measurement in accordance with the most recent ICSH guidelines (ICSH, 1993), resulting in a decline in the international standardization and comparability of the ESR.

HISTORY OF ESR STANDARDIZATION

ICSH-1973

The first reference method (ICSH, 1973) was described using 4 volumes of blood to 1 volume of filtered solution of trisodium citrate dihydrate ($Na_3C_6H_5O_7.2H_2O$) (38.8 g/l of sodium citrate in one litre of distilled water) as anticoagulant and measured with a Westergren-Katz glass tube of 300 mm length, clearly marked and numbered in steps of 10 units or less from 0 to 200 units. The internal pipette diameter was stated as 2.55 ± 0.15 mm. The ESR was expressed as ESR (Westergren 1 h) = x mm.

ICSH-1977

In the year 1977 (ICSH, 1977), the ICSH described a standardized selected method for measurement of the ESR to provide an international guideline. The main reason for the new method was the acceptance that the reference method described in 1973 was inconsistent. The description of the new method was the same as that of ICSH-1973. The most important point in the updated version was that it was acceptable, for routine methods, to use plastic pipettes and EDTA (as dipotassium or tripotrassium salt of ethylenediamine tetra-acetic acid) anticoagulated blood diluted, in the exact proportion of 4 volumes of blood to one volume of diluent, with citrate solution ($Na_3C_6H_5O_7.2H_2O$: 109 mM; 32.8 g/l of sodium citrate in 1 l of distilled water) or 9 g/l sodium chloride ('physiological solution') as an alternative to citrate anticoagulated blood. The ESR had to be expressed as follows: ESR (Westergren 1 h) = x mm.

ICSH-1988

The third ICSH paper regarding the ESR was published in 1988 (ICSH, 1988). This publication stated that it was not possible to recommend a definitive reference method. In this publication, the ICSH ESR expert panel introduced a standardized method for comparability with routine (or selected) methods. The standardized method used undiluted blood samples of packed cell volume (PCV) in the range 0.33 ± 0.03 under standardized conditions in a Westergren tube that met ICSH specifications (ICSH, 1973). The comparability with the routine method had to be performed with 10 samples with a range from 15 to 105 mm/1 h. The results for the routine method were related to the undiluted ESR as follows: routine Westergren method = (undiluted Westergren method × 0.86)−12. The results had to be given as mm/1 h.

ICSH-1993

The last review of ICSH recommendations for measurement of erythrocyte sedimentation rate was published in 1993 (ICSH, 1993). This document established

that the term erythrocyte sedimentation rate (ESR) was retained because of traditional usage, although a single measurement after 60 minutes is not a rate. The uses of undiluted EDTA samples with a PCV of 0.35 or less was recommended for performing the reference method. The standardized method was described as the same as the reference method with the only exception that glass and certain plastic pipettes could be used for the traditional Westergren method. The main reason for both methods was to use them for verification, quality control and to establish comparability of the results obtained with routine (working, selected) methods. This paper described very clearly that the reference values and the ESR results had to be expressed as for diluted blood at 60 min or normalized to 60 min. For comparison of results between the reference and standardized method and the routine method, the formula – routine Westergren method (diluted) = (undiluted Westergren method × 0.86)−12 – must be used (ICSH 1988). ICSH-1993 also included a table for accepting the results of any comparability as correct and stated that the results should be expressed as ESR = x mm.

Other standardization documents

Parallel documents were published by the NCCLS (1993) and its successor the CLSI (2000), as well as by various national standards authorities, *inter alia* in the BSI (1987) in the United Kingdom and the DIN (1997) in Germany. WHO (1993) has also published a technical 'broadsheet' describing the ICSH standard, intended especially for under-resourced countries. The CLSI (2010) document was recently revised, and International Standardization Organization (ISO) is in train to establish an international standard based on the BSI standard.

CLINICAL APPLICATIONS OF THE ESR

The ESR test is a laboratory test that serves as a general sickness index in conjunction with the patient's clinical history and physical examination findings (Koepke, 2002a). Therefore, it has been a popular procedure for many years, as it is useful to have this information available to the physician quite quickly after seeing the patient to decide on appropriate steps for care (Koepke, 2002b).

A search in PubMed (from 1921 to 2010) citation index identified 16386 papers that used the term ESR. The ESR does not measure an analyte but rather a physical phenomenon that depends on a large number of variables. The ESR is a nonspecific screening test used to detect the acute phase inflammatory response (Bain, 1983; Lewis, 2006; Briggs, 2009) and to monitor chronic processes (Zlonis, 1993). The test is mainly influenced by proteins (Gabay & Kushner, 1999), room temperature (Manley, 1957) and the presence of anaemia, which cause a false high reading, although some publications give a formula to correct the results (Fabry, 1987).

The usefulness of the ESR has been widely debated in the literature for many years (Weinstein & Del Giudice, 1994; Saadeh, 1998; Plebani, 2003). Its clinical utility has been demonstrated in editorial papers (Brigden, 1999; Brigden & Heathcote, 2000; Reinhart, 2006) and in reports concerning primary care assistance (Sox & Liang, 1986; Gronlie & Hjortdahl, 1991; Thue, Sandberg & Fugelli, 1994), the elderly (Kat *et al.*, 1989; Smith & Samadian, 1994; Stevens, Tallis & Hollis, 1995), hospital patients (Lluberas-Acosta & Schumacher, 1991; Olshaker & Jerrard, 1997), haematological malignancies (Haybittle *et al.*, 1985; Alexandrakis *et al.*, 2003), stroke (Vila & Chamorro, 1995), heart disease (Gillum, Mussolino & Makuc, 1995; Erikssen *et al.*, 2000; Rapaport, 2000; Wu *et al.*, 2002; Danesh, 2004), rheumatoid arthritis (Combe *et al.*, 2001; Wolfe & Pincus, 2001), giant-cell arteritis (Zweegman, Makkink & Stehouwer, 1993; Nuenninghoff *et al.*, 2003; Trejo-Gutierrez, Larson & Abril, 2008), spondylitis (Spoorenberg *et al.*, 1999), renal carcinoma (Ljungberg, Grankvist & Rasmuson, 1995), prostatic cancer (Johansson *et al.*, 1992a,b), rheumatic polymyalgia (Salvarani *et al.*, 2005) infection (Greidanus *et al.*, 2007; arthroplastia (Austin *et al.*, 2008), anaemia (Robins, Khan & Atrak, 2003; Winsor & Burch, 1994) and other diseases. Nowadays, it seems that many physicians worldwide use the clinical utility of this test, with intrinsic limitations, for diagnostic purposes or general screening of patient health.

REVIEW OF THE LITERATURE: USE OF THE ESR REFERENCE AND STANDARDIZED METHODS

Since 1991, many evaluations of new ESR analysers have been published. Very few of these publications

used the reference method with undiluted EDTA samples (Caswell & Stuart, 1991; Plebani *et al.*, 1998; Ozdem *et al.*, 2006) and did not apply the comparison table included in ICSH-1993. The formula from ICSH-1993 is used to compare the results of reference and standardized methods with the instruments, which always give the results as values of diluted samples as recommended by ICSH-1993. In most evaluations, new analyser methods were compared with the standardized method with diluted samples (Thomas & Karpic, 1993; Happe *et al.*, 2002; Romero, Munoz & Ramirez, 2003; Al-Fadhli & Al-Awadhi, 2005; Ajubi, Bakker & van den Berg, 2006; Mahlangu & Davids, 2008; Shelat, Chacosky & Shibutani, 2008; Alexy, Pais & Meiselman, 2009; Hardeman *et al.*, 2010a,b; Perovic, Bakovic & Valcic, 2010). As an example, in one paper (Cha *et al.*, 2009) undiluted samples and glass pipette were used for reference method when comparing with an analyser which gives the results as diluted samples. The conclusion of this study was that the Westergren method did not perform as well as the analyser. However, this conclusion is invalid, because of a failure to correct the results of undiluted samples according to the ICSH-1993 guidelines. This problem has occurred in other papers when discussing the Westergren method (reference/standardized) because the authors use this name generically whether using undiluted or diluted samples, glass or plastic pipettes and manual or semi-automated methods.

EVALUATION OF NEW ANALYSERS

Nowadays, the traditional Westergren method is not generally used in routine laboratories except in some developing countries. Many new technologies and analysers have been developed for measurement of the ESR (Caswell & Stuart, 1991; Plebani *et al.*, 1998; de Jonge *et al.*, 2000; Piva *et al.*, 2001; Happe *et al.*, 2002; Al-Fadhli & Al-Awadhi, 2005; Ozdem *et al.*, 2006; Osei-Bimpong, Meek & Lewis, 2007; Mahlangu & Davids, 2008; Shelat, Chacosky & Shibutani, 2008; Alexy, Pais & Meiselman, 2009; Perovic, Bakovic & Valcic, 2010). Some of these involve automation of the Westergren method with diluted or undiluted samples while others use very new technologies. The latter tend to use undiluted EDTA samples for ease of use, economy, practicability, closed sample manipulation and speed. The systems that give the results as Westergren method with diluted blood at 60 min or normalized to 60 min as recommended by ICSH-1993 are the only ones that have clinical value. It is important to recognize that the Westergren method is a specific test for the ESR. Other equivalent tests must establish their own normal reference ranges and levels of clinical utility, sensitivity and specificity.

ICSH REFERENCE METHOD FOR MEASUREMENT OF THE ESR

Aim

In the year 1993, the ICSH proposed reference and standardized methods, using undiluted EDTA anticoagulated samples, with haematocrit of 0.35 or less under standardized conditions in a Westergren open-ended glass pipette that meets ICSH-1993 specifications (ICSH 1993). Comparison of the results obtained by routine (selected, working) methods was by means of a formula and a table. This was a significantly revised version of the previous ICSH recommendations and was intended to provide a reference method for verifying the reliability of any modification of the test used in practice, especially new technologies. This ICSH method required the test to be carried out on EDTA blood not diluted in citrate, using specified Westergren tubes and using an experimentally derived formula for correction. This enables a correction chart to be compiled, and any new method could be considered satisfactory if 95% of results on samples at any measured ESR were within the reference range. However, this technique and the interpretation of the acceptable range for any routine method have been found to be a much more complicated procedure, unlikely to be universally adopted in practice.

Because of the misleading interpretations of the reference method and the confusion as to how to use the standardized method, the ICSH expert panel has established changes of the recommendations for the reference method and eliminated the standardized method.

ICSH confirms that the term Erythrocyte Sedimentation Rate (ESR) is retained because of traditional usage and to prevent confusion although, as stated above, a single measurement after 60 min is not a rate. It has been suggested (Plebani *et al.*, 1998; Piva *et al.*, 2001)

that the name ESR should be changed to Length Sedimentation Reaction in Blood (LSRB) but other authors are not of the same opinion (Hardeman, 2007a,b). The ICSH does not accept the suggested new name.

Blood sample

Blood should be obtained by clean venepuncture over a maximum period of 30 seconds. A manual or vacuum extraction venepuncture can be used, and the blood should be taken into EDTA (K_3 or K_2) anticoagulant (dilution <1%) or in sterile trisodium citrate dihydrate ($Na_3C_6H_5O_7.2H_2O$). Prior to testing, the EDTA samples should be diluted with sodium citrate ($Na_3C_6H_5O_7.2H_2O$) in the proportion of 4 volumes of blood to 1 volume of citrate. Blood samples may be drawn into sodium citrate directly, diluted in the proportion of rate of 4 volumes of blood 1 volume of citrate. Blood citrate samples can be stored for up to 2 h at ambient temperature or 4 h at 4 °C prior to testing.

Mixing of blood sample

For standard blood collection tubes, there should be a minimum of eight complete inversions with the air bubble travelling from end to end of the tube. Mixing should be continued until immediately before the ESR pipette is filled at the start of the test.

Sedimentation pipette specifications

ESR pipettes must be disposable but, in special situations, glass pipettes can be reusable after washing and drying properly. Glass or plastic pipettes may be used but, if plastic, should not show adhesive properties towards blood cells and should not release plasticizers that affect blood or alter sedimentation. The pipettes should be colourless, circular and of sufficient length to give a 200-mm sedimentation scale. The pipette diameter must be not <2.55 mm (no upper limit is specified but the volume of blood required should be minimized). The bore has to be constant (within 5%) throughout its length.

The pipette should be filled with anticoagulated blood to a level of at least 200 mm. During the sedimentation period, and during subsequent disposal, the system must prevent blood spillage or aerosol generation.

Pipette holding device

The pipette should be held vertically, protected from direct sunlight, draughts and vibration and kept at a constant temperature (±1 °C) within the range 18–25 °C during the sedimentation period.

Expressing the result

The results should be recorded as sedimentation occurring at 60 min from the beginning of test and expressed as ESR = x mm.

Comparability between ICSH reference method and routine method

All new technologies, instruments or methodologies must be evaluated against the Westergren reference method before introduction into clinical use. The new technology must be tested over a range of ESR values of 2–120 mm. In the 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 three different groups of values: 1–20, 21–60 and more than 60 mm. The main reason for this is that some papers have described incorrect high values in some new methodologies (Horsti, 2001; Ismailov, Shevchuk & Khusanov, 2005; Hardeman *et al.*, 2010a,b). The statistical methods recommended for ESR evaluations are the coefficient of correlation, the Passing-Bablock regression (Passing & Bablok, 1983, 1984) and the Bland-Altman statistical method (Bland & Altman, 1986).

Reference values

Reference values should be established locally in accordance with the ICSH recommendations on reference values (ICSH, 1978; International Federation of Clinical Chemistry [IFCC] and ICSH, 1987) and expressed in terms of results obtained with diluted blood. In view of the progressive rise in ESR with age, separate values should be established for each decade of adult life in males and females (Sharland, 1980; Nayha, 1987; Lewis, 2006; Osei-Bimpong, Meek & Lewis, 2007). The ICSH does not accept results obtained with undiluted blood samples as reference ESR values (Piva *et al.*, 2001). Several other clinical

variables influence the ESR and may therefore affect physiological reference values, most notably haemoglobin concentration, medication, menstrual cycle, pregnancy and smoking (Miao, 2002).

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