IRON STUDIES STANDARDISED REPORTING PROTOCOL

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RCPA
The Royal College of Pathologists of Australasia

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Scope

This protocol contains recommendations and guidelines for pathologists and pathology laboratories for the preparation of structured reports for iron studies.

Structured reporting aims to improve the completeness and usability of pathology reports for clinicians and improve decision support for patient management.

Whilst the wording of reports remains the intellectual property of each individual laboratory, these guidelines aim to ensure clear, concise and authoritative reports. They have been developed in response to extensive consultation within the medical and lay community conducted under the aegis of the National Blood Authority's Patient Blood Management program.

Workshops conducted in 2010 and 2012 identified a number of barriers to the identification and management of iron deficiency. Among these was the perceived lack of uniformity between pathology providers in cited Reference Intervals for Iron Studies and the language used to comment upon the numerical results.

A Working Group of Pathologists was convened by the RCPA and formed its definitive recommendations in February 2012. Please note that these recommendations and guidelines will not cover all cases. Conclusions and recommendations should be based on all evidence available to the reporting pathologist, including past results, history and any consultations with the referring clinician.

Membership and affiliations of the members of this Working Group is listed under *Authority and Development*.

In this updated edition of the reporting protocol, commenting around acute iron poisoning has been removed as this acute emergency should not rely on report commenting but rather be managed with real time notification. This working party is conscious that guidance on this matter falls within the scope of the RCPA-AACB High Risk Results Working Party.

Definitions

The list below provides definitions for general or technical terms used in this protocol.

Patient Data	Unique identifying data on the patient, including name, Medical Record Number or other assigned identification codes *plus* as much demographic data (age, sex and ethnicity) as is supplied on the request form.
Clinical information	Patient information required to inform pathological assessment, usually provided on the specimen request form.
Numerical results	Numerical results are those produced by properly calibrated and monitored laboratory assays. In the case of iron studies, these parameters typically include serum ferritin, iron and transferrin. All are measured directly and transferrin Saturation is derived from the measured parameters. Consensus has not been reached on the proper interpretation of other numerical results for assessing iron status such as soluble transferrin receptors and hepcidin levels. These methods will not be discussed in this edition of the Guidelines.
Cut-offs	Cut-offs, also called action points or decision limits, are concentrations that assist with diagnosis or the exclusion of a pathological process. It is at these cut-offs that a clinical decision is made. Cut-offs are not population derived reference limits.
Conclusions	It is recommended that commentary on the numerical results be worded as ‘Conclusions’.
Recommendations	If the history as stated and laboratory findings lead to the conclusion that the patient has abnormal findings, these Guidelines favour the strongly worded term “Recommendations”, rather than indecisive terms such as “Suggest”. If the report concludes that there is no evidence of either iron deficiency or iron overload, no recommendations should be added. Some pathologists are reluctant to make recommendations for patient care, confining their recommendations to further pathological testing, if any. This is a matter for individual judgement.

Introduction

Clinicians responsible for direct patient care depend upon the pathology laboratory for precise measurements as well as clear guidance as to the significance of these numerical results. These Guidelines are intended to assist pathologists and pathology laboratories provide standardised reports of iron studies for this purpose.

Iron deficiency, whether accompanied by anaemia or not, is a debilitating state. In young children it has been shown to impair cognitive development. (Lozoff and Georgieff 2006) In older children it causes cognitive and behavioural problems that can be reversed by iron supplementation. (Idiradinata and Pollitt 1993) In adults it is a common cause of physical and intellectual under-performance. (McClung, Karl and Cable 2009)

Iron depletion is evidence of a negative iron balance. In all cases of iron deficiency, a source of blood loss should be sought unless the patient has an extremely iron deficient diet. In adult males and post-menopausal females, iron deficiency is found to be associated with a thirty-fold increase in the incidence of colorectal cancer. (Ioannou, Rockey, Bryson, & Weiss, 2002)

Iron overload may be a clue to the presence of genetic haemochromatosis. The frequency of the serious haemochromatosis-associated allele *Cys*-282-*Tyr* in populations of Anglo-European descent is 1:20, making haemochromatosis due to homozygous *Cys*-282-*Tyr* one of the commonest inherited diseases. (Olynk, Cullen, Aquilia, Rossi, Summerville, & Powell, 1999) As untreated haemochromatosis can cause cirrhosis and hepatocellular carcinoma, identifying iron overload is an important public health issue.

Benefits of standardised reporting

The benefits of standardised structured pathology reports for cancer with standardised definitions for each component have been shown to significantly enhance the completeness and quality of data provided to clinicians and have been recommended both in North America and the United Kingdom. (Cross, Feeley and Angel 1998) (Mathers, et al. 2001) (Srigley, et al. 2009) (Gill, et al. 2009)

The College of American Pathologists and the Royal College of Pathologists (UK) have published useful protocols for the reporting of cancer. (College of American Pathologists 2012) The RCPA has also developed Structured Cancer Reporting Guidelines and in association with the Australasian Association of Clinical Biochemists (AACB) developed Guidelines for standardised reporting of serum protein electrophoresis.

Formatting of pathology reports

Good formatting of the pathology report is essential for optimising communication with the referring clinicians (Valenstein 2008). The report should be formatted to provide information clearly and unambiguously to the treating doctors and should be organised with their use of the report in mind.

To reduce confusion among referring clinicians, uniformity should be sought in all aspects of reporting. This includes the tests provided, their sequence on the page, the number of significant figures reported, units and reference intervals. Ideally, results should be directly comparable with inclusion of reference intervals and cut-offs in use. This Guideline sets out a standardised format for the reporting of iron studies.

Authority and development

Protocol developers

This revised protocol was developed by an expert committee, with assistance from relevant stakeholders.

Expert committee

- Dr Emad Abro, Princess Alexandra Hospital
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- Dr Mohamed Saleem, Royal Adelaide Hospital
- Mr Greg Ward, Sullivan Nicolaides Pathology
- Dr Helen Freeborn, Deputy Chief Executive Officer, RCPA

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- Mr Sailesh Ram, Health Economist, RCPA

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Development process

This protocol has been developed using methods and format set out in Guidelines for Authors of Structured Cancer Pathology Reporting Protocols (The Royal College of Pathologists of Australasia 2009). Where no reference is provided, the authority is the consensus of the Working Group.

Pre-analytical

When considering iron deficiency, overload or toxicity, the clinician will generally request "iron studies", which should be regarded by the pathology laboratory as serum "Ferritin, iron, transferrin and transferrin saturation". For confirmation of suspected iron deficiency, clinicians should be encouraged to request serum ferritin, with C-Reactive Protein if there is clinical indication of inflammatory condition (see later).

Requestors should include relevant clinical notes and particularly state if:

- there has been a recent blood transfusion or iron infusion. Iron studies are unreliable for several days after blood transfusion and the ferritin level can remain elevated for 2-3 months after intravenous iron infusion.
- The patient is pregnant.
- There is a relevant family history of hereditary haemochromatosis
- The patient is undergoing venesection for iron overload

Serum is the nominated sample type for the purposes of this document, but heparinised plasma may also be used if supported by the assay manufacturer's claims or other validation data. Other anticoagulants are unsuitable as they chelate iron.

Fasting samples are preferred due to the diurnal variation of circulating iron, unless a ferritin level is requested on its own.

This section relates to standard information that should be recorded on receipt of the specimen in the laboratory.

1. The RCPA Guideline The Pathology Request-Test-Report Cycle — Guidelines for Requesters and Pathology Providers must be adhered to. This document specifies the minimum information to be provided by the requesting clinician for any pathology test.

2. All demographic information provided on the request form and with the specimen must be recorded. The patient's ethnicity should be recorded, if known, particularly whether the patient is of Aboriginal, Torres Strait islander or Maori origin. This is in support of government initiatives to improve the health of indigenous populations.

3. Patient data may include the patient's name (family and given names), Medical Record Number, date of birth, address and/or Individual Healthcare Identifier.

4. All clinical information as documented on the request form must be recorded verbatim where clearly legible.

5. The request information may be recorded as a single text (narrative) field or it may be provided by secure electronic link.

6. The pathology accession number of the specimen must be recorded.

7. The principal clinician involved in the patient's care and responsible for investigating the patient must be recorded.

8. Any clinical information received in other communications to or from the requestor or other clinician should be recorded.

Numerical results

The following parameters should be reported when “iron studies” are requested: ferritin, iron, transferrin and transferrin saturation, in that order. Current information from the RCPAQAP indicates that the majority of enrolled laboratories measure and report serum transferrin. A minority of laboratories continue to report Total Iron Binding Capacity (TIBC) although this may be calculated from transferrin rather than measured.

Ferritin is the most important measure in determining iron deficiency and it is recommended that ferritin be given prominence as the first parameter reported.

It is recommended that:

- Ferritin concentration is reported in micrograms per litre (ug/L).
- Iron concentration is reported in micromoles per litre (umol/L).
- Transferrin concentration is reported in grams per litre (g/L).
- To align with the proposed recommendation of the AACB Harmonisation Working Party (personal communication with Chair of Calculated Parameters Working Party), the recommended formula for calculating Percent Transferrin Saturation is: 3.982 X Iron (umol/L) / Transferrin (g/L).

Appendix A reports the findings of a recent commutability study performed on 11 current assay-instrument configurations for ferritin measurement. For a serum pool with a median reported result of 22 ug/L, results ranged from 20-37 umol/ with different laboratory method. Inter-method bias has also been demonstrated by the RCPAQAP Liquid Serum Chemistry Program where in 2019, a sample with a median reported ferritin of 761 ug/L had a range of 603 to 895 ug/L across 4 instrument platforms.

It is important for laboratories to assess and understand any biases of their assays before deciding to adopt these cut-offs or modify them. Serum-based correlations are preferred over the use of quality assurance/control material in any assay correlations.

Cut-offs and Reference Intervals

- Serum ferritin levels greater than or equal to 30 ug/L up to the method-related upper reference limit demonstrate healthy iron stores as long as co-existing inflammatory disease or hepatocellular damage are not present. (Lipschitz, Cook and Finch 1974)

- A serum ferritin level less than or equal to 20 ug/L for pre-pubescent children (with or without anaemia) is diagnostic of iron deficiency.

- A serum ferritin level of less than 30 ug/L for an adult is diagnostic of iron deficiency.

- Serum ferritin concentrations typically fall in the last 4 weeks of normal pregnancy. This reflects transfer of organic iron from mother to foetus, rather than any change in iron metabolism. However, a ferritin concentration around 30 g/L or less is still considered diagnostic of iron deficiency at any stage of pregnancy.

- Serum ferritin levels greater than 20 ug/L in an anaemic pre-pubescent child or greater than 30ug/L in an anaemic adult may represent iron deficiency if there is coexisting inflammatory disease.

  Ferritin is an acute phase protein and its levels can be elevated in the setting of inflammation or other pathology. In a systematic review of non-healthy population studies correlating ferritin with bone marrow iron stores, the mean ferritin concentration was reported to range from 82ug/L to 158ug/L for iron depletion, with wide variation depending on the underlying pathology (Maria Garcia-Casal 2018).

- It is acknowledged that while a low ferritin is consistent with iron deficiency, various ferritin levels from <15 to 30 ug/L have been found to correlate with absent bone marrow stores (Maria Garcia-Casal 2018).

- Individual laboratories may choose to vary their lower cut-off to reflect how their assay method compares to published results from other assay methods.

- Isolated reduction of serum iron is of dubious significance given the wide variability of serum iron concentrations.

- A raised percentage transferrin saturation in isolation may be the earliest indicator of iron overload.

- An elevated ferritin concentration above the method-related upper reference limit may be due to concurrent inflammatory disease, liver disease or iron overload.

- There is no recommended harmonised upper reference interval value for ferritin as significant variation exists between methods. Expected values for the upper reference interval quoted by manufacturers of some commonly used assays range from 275 to 400 ug/L (male adults) and 150 to 307 ug/L (female adults). Laboratories are encouraged to report upper reference intervals derived using their assay methodology from a healthy population without liver or renal disease, alcohol over-use, iron overload, inflammatory conditions or malignancy, and with consideration towards a normal body mass index (BMI).

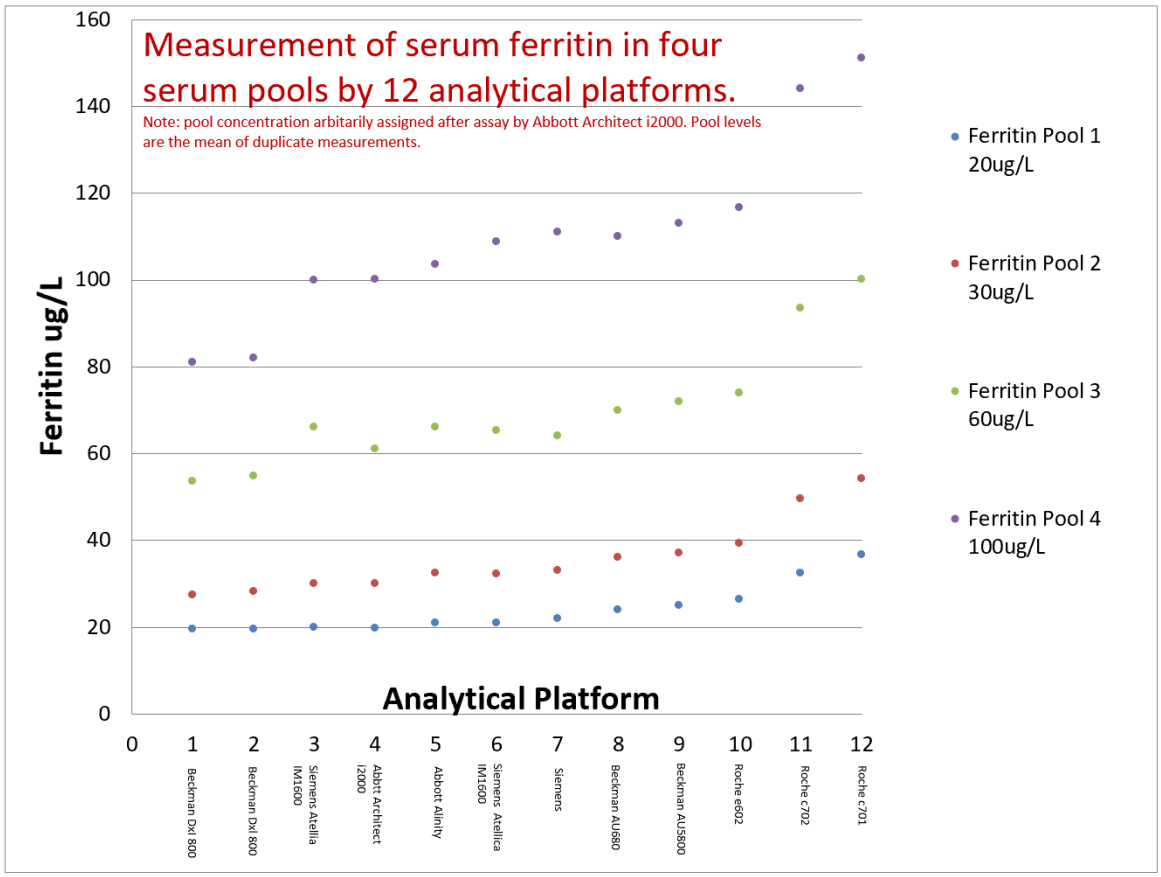
Recommendations

Below are suggested recommendations to include in a Structured Report on Iron Studies:

Result	Recommendations
Ferritin less than 20 ug/L in a child <16 years (or pre-pubescent child)	Results consistent with iron deficiency. In children this is usually due to either dietary problems or recent rapid growth and can cause significant neuro-cognitive impairment. Recommend oral iron therapy for 2 to 3 months then re-check serum ferritin and haemoglobin if indicated.
Ferritin less than 30 ug/L in a woman 16-50 years (or “of reproductive age” as determined by the laboratory)	Results consistent with iron deficiency. This may be in association with multiparity or heavy menstrual loss, but consider gastro-intestinal blood loss.
Ferritin less than 30 ug/L in a man or woman >50 years	Results consistent with iron deficiency. Gastro-intestinal evaluation for a source of blood loss should be considered.
Ferritin levels 30 -upper limit in adult 20-upper limit in child	Low normal and normal ferritin levels may be seen in iron deficiency where there is concomitant inflammation. If clinically indicated repeat with CRP level. In some cases of known chronic illness where CRP is not elevated eg in the immuno-compromised, this concentration of serum ferritin is inconclusive.
Elevated Ferritin > upper limit with or without Transferrin saturation greater than 45%	Elevated ferritin may be associated with liver disease, metabolic syndrome, chronic alcohol use, inflammation, iron overload or malignancy. Where cause is unclear, recommend repeat measurement in 3-6 months. Increasing or very high concentrations warrant further investigation. Note: Genetic testing for Hereditary Haemochromatosis is recommended in first degree relatives of diagnosed individuals, or those with persistent elevations of ferritin and/or transferrin saturation.
Transferrin saturation greater than 45% without elevation in Ferritin	Genetic testing for Hereditary Haemochromatosis is recommended in first degree relatives of diagnosed individuals, or those with persistent elevations of ferritin and/or transferrin saturation.

Appendix A

Findings of recent commutability study



Source: Data from seven participating laboratories: Alfred Pathology Service, Austin Pathology, Dorevitch Pathology, Melbourne Pathology, Pathology Queensland, Queensland Medical Laboratory and Sullivan Nicolaides Pathology.

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