IRON STUDIES STANDARDISED REPORTING PROTOCOL

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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*.

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 instruments. In the case of iron studies, these parameters usually include serum ferritin, serum iron and serum transferrin. These are all measured directly. Transferrin Saturation is derived from the directly measured parameters. Other numerical results of assessing iron status are in development, but consensus has not yet been reached on their proper interpretation. These include soluble transferrin receptor and hepcidin levels. These developmental 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.

The guidelines also provide recommendations for investigating suspected acute iron poisoning.

Benefits of standardised reporting

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 recently published useful protocols for the reporting of cancer. (College of American Pathologists 2012) The RCPA has also developed Structured Cancer Reporting Guidelines and recently 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 clinician. (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. In this sense, the report differs from a laboratory checklist, which is organised with the pathologists' workflow as a priority.

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 and appropriate for the reference intervals and cut-offs in use. This Guideline sets out a standardised format for the reporting of iron studies.

Authority and development

This section provides details of the committee involved in developing this protocol and the process by which it was developed.

Protocol developers

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

Expert committee

- Que Lam, Scientific and Regulatory Affairs Committee, AACB
- Cameron Martin, National Standing Committee - GP Advocacy & Support, RACGP
- Lilon Bandler, Faculty of Medicine, University of Sydney
- Steve Flecknoe-Brown, Anaemia Management Working Group, National Blood Authority
- Samarina Musaad, Chemical Pathology Advisory Committee, RCPA
- Bronwyn Williams, Haematology Advisory Committee, RCPA
- James Daly, Haematology Advisory Committee, RCPA
- Debra Graves, Chief Executive Officer, RCPA

Acknowledgements

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Secretariat

- Debra Graves, Chief Executive Officer, RCPA
- Sailesh Ram, Health Economist, RCPA

Medical editor

- Bronwen Ross, Deputy Chief Executive Officer, RCPA

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).

Serum is the nominated sample type for the purposes of this document but heparinised plasma may also be used if supported by the instrument maker'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 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 Pathology Request-Test-Report Cycle — Guidelines for Requesters and Pathology Providers" (The Royal College of Pathologists of Australasia 2010), 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.

9. 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.

Numerical results

The following parameters should be reported when “iron studies” are requested: ferritin, iron, transferrin and percent transferrin saturation, in that order. There is no role for reporting Total Iron Binding Capacity (TIBC).

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).
- Transferrin saturation is calculated from iron and transferrin results and reported as per cent (%).

While some recommendations in this document have been made based on specific numerical cut-offs it is acknowledged, especially in the case of ferritin measurement, that results will vary between assays due to analytical differences. 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 demonstrates 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 levels of 20-60 ug/L in an anaemic pre-pubescent child may represent iron deficiency if there is coexisting inflammatory disease.

- Serum ferritin levels of 30-100 ug/L in an anaemic adult may represent iron deficiency if there is coexisting inflammatory disease.

- 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.

- In suspected iron poisoning serum iron concentrations less than 55 umol/L between 1 and 6 hours post ingestion do not usually produce any clinical problems. Levels in the 55 - 310 umol/L range are associated with clinically mild iron poisoning. Concentrations greater than 310 umol/L are associated with liver toxicity. (Robertson and Tenenbein 2005)

- Serum ferritin concentrations typically fall in the last 4 weeks of normal pregnancy. This reflects transfer of organic iron from mother to fetus, rather than any change in iron metabolism. However, a ferritin concentration around 30 ug/L or less is still considered diagnostic of iron deficiency at any stage of pregnancy. As for non-pregnant individuals, ferritin concentrations in the 30-100 ug/L range could indicate iron deficiency in the presence of co-existing inflammatory disease.

As there is some inter-assay variation with ferritin levels around the 20-30 ug/L range, individual laboratories may choose to vary their cut-off to reflect how their assay method compares to published results from other assay methods – eg less than or equal to 33ug/L in an adult.

Conclusions

The following statements should be included in all pathology reports for iron studies as the conclusion (ie as commentary on the history as stated and laboratory findings).

Numerical results	Conclusion
Serum ferritin concentrations within reference interval in the absence of clinical or laboratory evidence of inflammation	No evidence of iron deficiency
Ferritin less than 20 ug/L in a pre-pubescent child or less than 30 ug/L in an adult	Confirmed iron deficiency
Borderline ferritin concentration (20 – 60 ug/L for pre-pubescent children and 30-100 ug/L for adults) with either anaemia, clinical history suggesting inflammatory disease or positive laboratory inflammatory markers	This result may indicate iron deficiency, as serum ferritin concentration can be elevated by inflammatory disease
Low serum iron with ferritin level within reference interval and no clinical or laboratory suggestion of inflammation	An isolated reduction in serum iron in isolation should never be reported as iron deficiency
Elevated serum ferritin concentration with transferrin saturation less than or equal to 45%	This result may represent iron overload, inflammation, organ damage (especially hepatic injury), malignancy or renal disease
Transferrin saturation greater than 45% with or without elevated serum ferritin concentration	Persistent elevations of transferrin saturation may be the earliest sign of iron overload
Serum iron less than 55 umol/L, in a specimen taken between 1 and 6 hours post ingestion	Unlikely to cause serious iron toxicity
Serum iron of 55 – 310 umol/L in suspected acute iron poisoning	Clinically significant iron toxicity
Serum iron greater than 310 umol/L in suspected acute iron poisoning	Severe iron poisoning likely to cause organ damage
Ferritin less than 30 ug/L in patients on therapeutic venesection	Low serum ferritin levels are the target of some therapeutic venesection programmes
Elevated serum iron within 2 weeks or elevated ferritin within 2 months of intravenous iron fusion	Elevated levels probably reflect effects of recent intravenous iron infusion

Recommendations

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

Result	Recommendations
Ferritin less than 20 ug/L in a non-anaemic pre-pubescent child	In children this is usually due to either dietary problems or recent rapid growth and can cause significant neuro-cognitive impairment (Sachdev, Gera and Nestel 2005). Follow up serum iron, transferrin, transferrin saturation, are not necessary. Recommend oral iron therapy for 6 weeks then re-check serum ferritin.
Ferritin less than 20 ug/L in an anaemic pre-pubescent child	In children this is usually due to either dietary problems or recent rapid growth and can cause significant neuro-cognitive impairment (Robertson and Tenenbein 2005). Follow up serum iron, transferrin, transferrin saturation, are not necessary. Recommend oral iron therapy for 3 months and then re-check haemoglobin and serum ferritin.
Ferritin less than 30 ug/L in a menstruating woman with or without anaemia	During the reproductive years, iron deficiency in women is usually due to multiparity or heavy menstrual losses. Investigation of the gastro-intestinal tract for a source of blood loss may be indicated.
Ferritin less than 30 ug/L in a man or post-menopausal woman with anaemia	Iron deficiency in men and post-menopausal women suggests abnormal blood loss. Gastro-intestinal evaluation for a source of blood loss should be considered. Follow up serum iron, transferrin, and transferrin saturation – are not necessary.
Borderline ferritin level (20 – 60 ug/L in a pre-pubescent child or 30-100 ug/L in an adult) with anaemia but no clinical history suggesting inflammatory disease and no elevated serum CRP	Recommend repeat with CRP level.
Borderline ferritin level (20 – 60 ug/L in a pre-pubescent child or 30-100 ug/L in an adult) with a clinical history suggesting inflammatory disease or an elevated serum CRP	In view of inflammation (as demonstrated by history or CRP) the ferritin level is inconclusive. Repeat ferritin level when the inflammation has subsided. Follow up serum iron, transferrin, and transferrin saturation are not necessary. 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 level with less than or equal to 45% transferrin saturation	Exclude ferritin elevation due to liver disease, renal impairment and inflammatory conditions. Where the cause is not known, recommend monitoring serum ferritin every 3 to 6 months. Progressively increasing or very high concentrations of serum ferritin warrant further investigation.
Elevated ferritin level or transferrin saturation greater than 45%, confirmed on two separate occasions	Recommend genetic testing for haemochromatosis. Genetic testing should be preceded by genetic counselling.
Serum iron level greater than or equal to 90 umol/L in suspected acute iron poisoning	Chelation therapy is recommended in acute iron poisoning if the patient is symptomatic or the serum iron level is greater than or equal to 90 umol/L (Madiwale and Liebelt 2006).

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