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RCPA
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Position Statement

Subject:	The Use of Iron Studies, Ferritin and Other Tests of Iron Status
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Introduction

Iron Deficiency (ID) is the commonest nutritional deficiency state in Australia. It is significantly under-diagnosed. There are major opportunities for individual and population health improvements through increased awareness, testing and targeted iron supplementation.

Non-anaemic ID (NAID) is increasingly recognised as a cause of under-performance. Iron replacement in ID is known to improve fatigue, exercise tolerance and cognitive function in children, adolescents and adults[1]. One study looking at the effect of iron stores in early pregnancy on pregnancy outcome found that babies of women with NAID weighed on average 192 g less than those of women with normal iron stores (P = 0.028). This was after adjusting for confounding variables and occurred despite all women being treated in accordance with standard antenatal iron supplementation policies[2].

Iron Deficiency Anaemia (IDA) is associated with impaired cognitive development in preschool-aged children and diminished work productivity, cognitive and behavioural problems in adults. Among pregnant women, IDA is associated with increased risks of low birth weight, prematurity and maternal morbidity. The impact of IDA on health has been conclusively documented in several Cochrane reviews[3,4,5].

Iron therapy with or without testing? People should not be treated with iron unless they have confirmed iron deficiency[6]. Genetic predisposition to iron overload is sufficiently common in Australia to make iron therapy hazardous without laboratory confirmation of iron deficiency. In our multi-ethnic population, there are many causes of microcytic anaemia (eg thalassaemia) that do not respond to iron supplementation.

Iron Overload is often overlooked: the clinical presentation is subtle and gradual. *Genetic haemochromatosis* is one of the commonest genetic diseases in persons of European descent.

[1] Pratt & Khan, 2015
[2] Ribot, Aranda, Viteri, Hernández-Martínez, Canals & Arija, 2012
[3] Reveiz, Gyte & Cuervo, 2011
[4] Zeng & Wu, 2007
[5] Pasricha et al., 2010
[6] Commonwealth Government Clinical Practice Guidelines, 2012

The Importance of Iron

Iron performs many functions in the body. It is well recognised as the core of haemoglobin, which carries oxygen from the lungs to the tissues. Iron also plays an important role in mitochondrial energy production and other cellular functions.

Iron is toxic to the body in its free state. The cells are protected from this toxicity by protein ligand binding or by the iron being incorporated into a ring-shaped porphyrin molecule.

The most significant form of iron is the organic ring known as *heme*. Heme iron is found in proteins connected with oxygen transport and trapping by the cells, including hemoglobin, myoglobin and mitochondrial cytochrome oxidases. Non-heme iron can be found in proteins connected with cellular energy production and in iron storage proteins like transferrin and ferritin.

Iron overload can damage vital organs.

Incidence of ID in Australia

Children: ID is the most common childhood cause of anaemia worldwide with the prevalence highest among preschool-aged children[7]. Because iron is widely administered to children with or at risk for ID, reliable data on the prevalence of true iron deficiency in the Australian pediatric population are not available[8].

Adult Female: Thirty-four percent of Australian women of child bearing age have ID[9]. In Australia 35.2% of new female blood donors or who have not donated in 2 years have ID[10].

Adult Male: In Australia 4.8% of new blood donors and those who have not donated in 2 years have ID. Males have a third the risk of ID as females[11].

Anaemia: Two to five percent of the adult males and post-menopausal women have iron deficiency anaemia[12]. Seventeen percent of an elective orthopaedic surgery population in SA were anaemic: half were iron deficient[13]. Australian evidence suggests that 60% of iron deficiency anaemia remains undiagnosed in tertiary settings[14].

Special Populations: Indigenous and refugee populations within Australia are more likely to have iron deficiency anaemia. Twice as many people whose main language spoken at home was not English have IDA compared with those whose main language is English. Those who were not in the labour force also have twice as much IDA as those who are employed[15].

The finding of ID or iron deficiency anaemia must be followed by a search for the cause.

ID is so common in women of child-bearing age that it is easy to attribute all cases in women to menstrual loss causing negative iron balance. Causes of ID fall into five groups:

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[7] Thompson, Biggs & Pasricha, 2013
[8] ibid
[9] Australian Bureau of Statistics (ABS), 2012
[10] ibid
[11] Salvin, Pasricha, Marks & Speedy, 2014 – data re-analysed in 2017 by authors
[12] Goddard, James, McIntyre & Scott, 2011
[13] *Internal Medicine Journal*, 2016. B. Kearney et al
[14] Fazal, Andrew, Thomas & Saffouri, 2017
[15] *British Journal of Nutrition* 2016, 115, 703–708

1. Chronic blood loss – either overt (menorrhagia, gastrointestinal haemorrhage, haemodialysis, blood donation) or occult (especially gut neoplasia);
2. Nutritional deficiency;
3. Malabsorption –especially atrophic gastritis, *Helicobacter* infection, coeliac disease;
4. Red cell damage due to extreme training in elite athletes and dancers; and
5. Genetic causes of iron deficiency and dysregulation of levels which have recently been discovered[16].

Iron Overload

Incidence in Australia – Elevated Ferritin levels (>300) are common and are seen in more than 20% of adult males over 30y and in 2.6% of all adult females (ranging from 0.5% in the 16-44y/o group, to more than 10% in the older than 55y group)[17].

Genetic haemochromatosis, leading to iron overload, is seen in 1 in 400 persons of European descent. This was confirmed in a large cohort of patients with elevated ferritin levels submitted to genetic testing in Australia. Of these, 6.2% were homozygous for the haemochromatosis-associated allele C282Y and 7.5% were compound heterozygous for C282Y and the less common allele H63D.

Iron overload due to genetic haemochromatosis can damage liver, pancreas ("bronze diabetes") and gonads and is a cause of primary liver cell cancer. Effective treatment negates these risks if the iron overload is detected early and treated by therapeutic venesection.

Causes of non-genetic iron overload include alcohol abuse, multiple transfusion, haematological disease, excessive oral iron intake and malignancy.

Requesting Strategies

Iron Studies (Iron, Transferrin, Transferrin Saturation and Ferritin) to identify iron deficiency or overload are appropriately requested in these patients:

- Suspected ID - those at increased risk of iron deficiency (poor diet, vegans, certain population groups, blood loss, coeliac disease), those with the characteristic symptoms of fatigue, poor concentration, decreased exercise tolerance, pica (especially ice) or in the presence of anaemia or other nutritional deficiencies;
- To avoid transfusion by detecting and correcting iron deficiency prior to surgery[18];
- As part of a routine antenatal testing strategy at the first antenatal visit and then as determined by result obtained; and
- Suspected iron overload: family history of genetic or phenotypic iron overload, liver disease, “bronze diabetes” and pseudogout.

Testing Strategies

Iron Deficiency in this position paper is defined as a ferritin level below 30ug/L (this also applies in pregnancy) or less than 20ug/L in prepubescent children[19].

A ferritin level of <15ug/L has a specificity of 99% but a sensitivity of only 75% for finding ID. In contrast a cutoff level of 30 ug/L has a sensitivity and specificity of 92 and 98%

[16] Camaschella, Pagani, Nai & Silvestri, 2016
[17] K Sikaris; personal communication, 2017. See Appendix B: age and gender related ferritin levels
[18] National Blood Authority *Patient Blood Management Guidelines,* 2012.
[19] RCPA Iron Studies Standardised Reporting Protocol, 2014

respectively. A cutoff of 41ug/L has a sensitivity and specificity of 98 and 98%. It is for this reason that the RCPA recommends laboratories use 30ug/L as the lower limit of the reference range for ferritin[20].
Anaemia is a late stage feature of ID. Testing when the patient has become anaemic will only detect a minority of ID patients. For example, a haemoglobin cutoff of 110g/L in first trimester patients detects only 7.5% of cases of iron deficiency[21]. When IDA is first encountered, it is usually normocytic, with microcytosis and hypochromia developing in advanced IDA[22].

Iron overload is always accompanied by a ferritin above the upper limit of the reference range. In many patients with moderately elevated ferritin levels this is due to other conditions such as inflammation, malignancy and liver disease.

Iron Studies: This is the appropriate testing strategy for individual "case finding" – in a person suspected of either iron deficiency or iron overload (acute, early or established). The interactive nature of the three components allows for more accurate interpretation.

Elevated or decreased **serum iron levels** often cause confusion. The only clinical situation in which a serum iron level is of value viewed in isolation is in suspected iron poisoning.

A better strategy is to report **transferrin saturation without iron concentration**. A low transferrin saturation in the setting of an equivocal ferritin level is suggestive of iron deficiency. An elevated transferrin saturation is the first manifestation of iron overload.

Ferritin: Ferritin should not be used in isolation except in these two specific circumstances: - monitoring treatment of known iron deficiency or iron overload or in a routine screening strategy such as antenatal testing. Co-existing inflammation will cause elevations in ferritin unrelated to iron status, as it is an acute phase reactant. In both monitoring and screening for iron deficiency ferritin levels >30ug/L should be interpreted in association with a measure of inflammatory response, such as C-reactive protein (CRP).

Soluble transferrin receptor (sTFR) may be used to confirm iron deficiency in anaemic patients with a serum ferritin of 30-100 ug/L and evidence of an inflammatory process. There are some inflammatory conditions, such as systemic lupus, which do not cause the CRP to rise. Pathologist guidance should be sought in these circumstances.

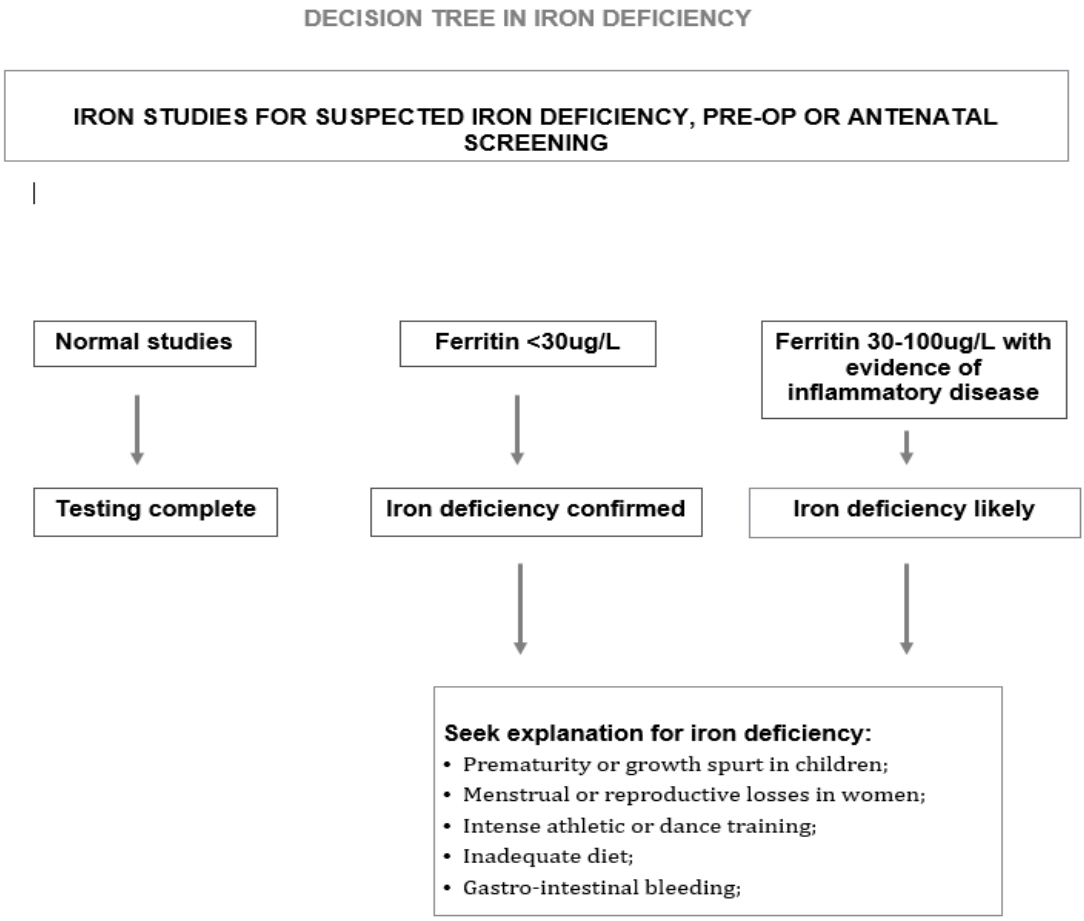
Haemoglobin response to iron therapy. Where doubt remains despite described testing strategies, and further invasive investigation of probable iron deficiency is not appropriate, e.g. advanced age or multiple co-morbidities, a trial of iron and assessing Hb and reticulocyte response to iron therapy may be of value.

Non-invasive methodologies (eg Ferriscan) are available to quantify iron liver loading. This may have diagnostic value in the presence of apparent biochemical overload in the absence of a known aetiology or to determine the need for therapeutic venesection.

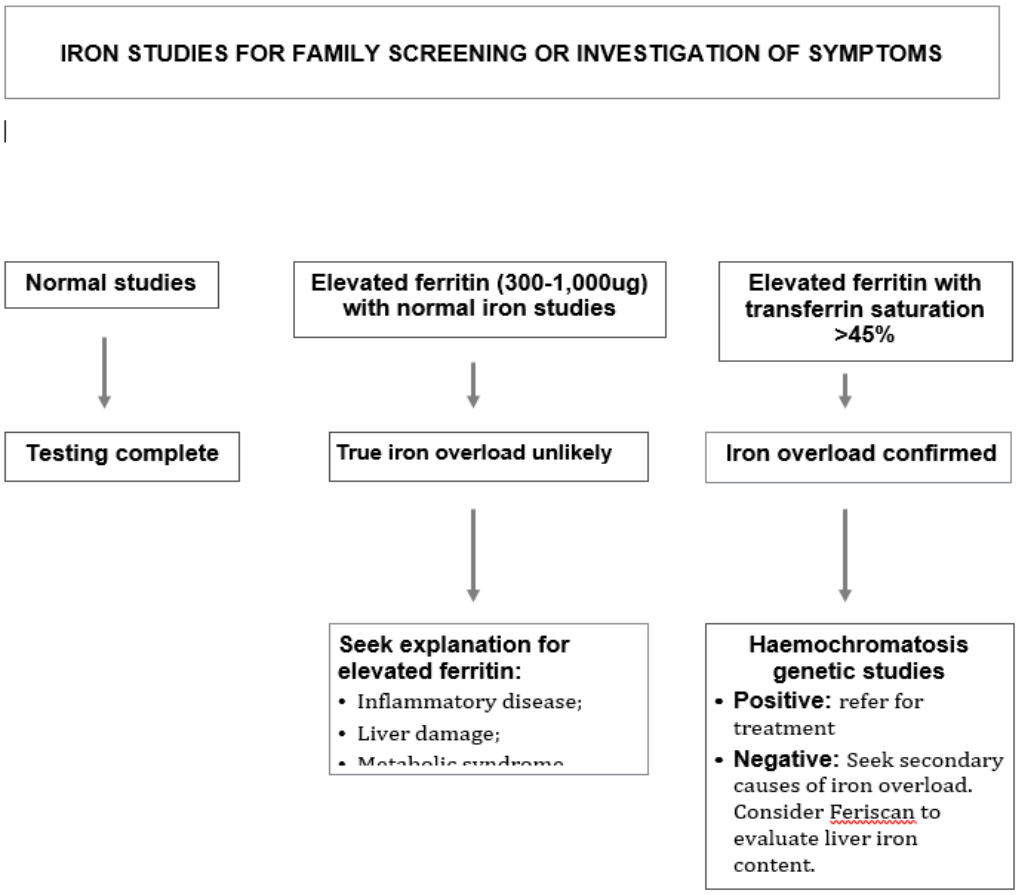
Reporting protocols: Laboratories should follow the RCPA's *Iron Studies Standardised Reporting Protocol, 2013*. Also, see Appendix A: *Decision Points*.

[20] ibid
[21] K Sikaris; personal communication, 2016.
[22] Schrier 2017

Appendix A: Decision Points



DECISION TREE IN SUSPECTED IRON OVERLOAD



Appendix B: Ferritin Results from 2,134,906 Australian Patients

Gender	Age	n	Fer <30	Fer >200	Fer >300	Fer >1000
F	<16	40,542	34.8%	1.5%	0.6%	0.0%
F	16-29	277,614	31.7%	2.1%	0.7%	0.0%
F	30-39	285,125	27.3%	3.3%	1.1%	0.1%
F	40-54	352,046	26.2%	6.9%	2.6%	0.2%
F	55-69	249,173	8.8%	20.9%	8.6%	0.7%
F	70-84	155,620	12.2%	23.8%	11.8%	1.3%
F	85+	108,896	13.2%	25.5%	14.4%	1.8%
M	<18	37,473	25.3%	2.2%	0.8%	0.1%
M	18-29	63,152	3.6%	23.3%	7.7%	0.3%
M	30-39	77,532	2.9%	42.2%	19.1%	0.8%
M	40-54	139,511	3.5%	51.7%	28.4%	1.6%
M	55-69	166,823	5.6%	48.6%	29.0%	2.5%
M	70-84	118,224	9.1%	38.3%	22.8%	2.7%
M	85+	63,175	9.5%	35.9%	21.9%	3.0%

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