The Newcastle upon Tyne Hospitals NHS Foundation Trust

Diagnosis and Management of Iron Deficiency in Adults with Cyanotic Congenital Heart Disease

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1 Introduction

Cyanosis, a bluish discolouration of the skin, typically presents when deoxyhaemoglobin levels rise above 5g/dl and arterial oxygen saturations are less than 85%. Cyanosis occurs in around 10% of adults with congenital heart disease [1]. These patients need tertiary care; however, they are often managed by physicians from a range of disciplines [2].

Chronic cyanosis leads to tissue hypoxia, which stimulates increased erythropoietin production in the kidney and a secondary erythrocytosis. This is a physiologically appropriate response to hypoxia in adults with congenital heart disease and maintenance of an appropriate erythrocytosis to enable adequate oxygen delivery to the tissues requires sufficient iron stores. However, over a third of cyanotic congenital heart disease patients are iron-deficient [3,4]. Causes include inadequate dietary intake, malabsorption and increased consumption in the context of secondary erythrocytosis, inappropriate venesection, haemoptysis, bleeding from AVMs or collaterals, gastrointestinal blood loss, menorrhagia, abnormal haemostasis and anticoagulants/anti-platelet use. Furthermore, chronic inflammatory states and increased hepcidin production impair the release of available iron stores, resulting in functional iron deficiency.

Whilst hyperviscosity in chronically compensated erythrocytosis is rare, iron deficiency itself may produce symptoms resulting from decreased tissue oxygen delivery that resemble, and are often confused with, those of hyperviscosity [4]. Therefore, every cyanotic patient presenting with hyperviscosity symptoms has to be evaluated for iron deficiency. Given the fact that iron deficiency might predispose to stroke and myocardial ischemia in adults with cyanotic CHD, phlebotomy may have harmful rather than beneficial effects in these patients [5,6]. Typical hematologic findings of an iron deficient state are microcytic and hypochromic red blood cells. In cyanotic CHD patients however, normocytosis and even macrocytosis are frequently found, possibly due to concomitant Vitamin B or folic acid deficiency [3]. Iron status should therefore be routinely and periodically assessed by measuring serum ferritin and transferrin saturation concentrations, and not by haemoglobin, packed cell volume, and erythrocyte indices alone. In addition, optimal haemoglobin levels correlate inversely with resting oxygen saturations [7]. Replacement of iron has been shown to improve quality of life, exercise tolerance and outcome in these patients [8,9].

2 Guideline scope

This guideline is intended for adults with congenital heart disease who are cyanotic (oxygen saturations ≤90%) in the setting of Eisenmenger syndrome, unrepaired complex disease, or surgical repairs where an iatrogenic or otherwise right to left shunt exists, e.g. Fontan circulation. The guideline is designed to support clinicians working within the congenital heart disease and pulmonary hypertension services. It also aims to highlight an often, unrecognised issue to other clinicians who may encounter these patients, for example in Accident and Emergency or adult cardiology services, and encourage the pursuit of specialist advice.

3 Main Body of the Guideline

Adults with congenital heart disease and cyanosis should be followed up, at minimum, on an annual basis [10-12]. Where possible, full blood count, ferritin, transferrin saturation, clotting profile, renal function and uric acid should be assessed. Folic acid and vitamin B12 should also be measured in the presence of iron deficiency with normal or elevated mean corpuscular volume [4]. Figure 1 provides a suggested flowchart for the investigation and management of iron deficiency in this group [13]. The possibility of iron deficiency and the need for treatment may also be considered in the context of recent haemorrhage or surgical intervention, and the presence of heart failure or chronic kidney disease.

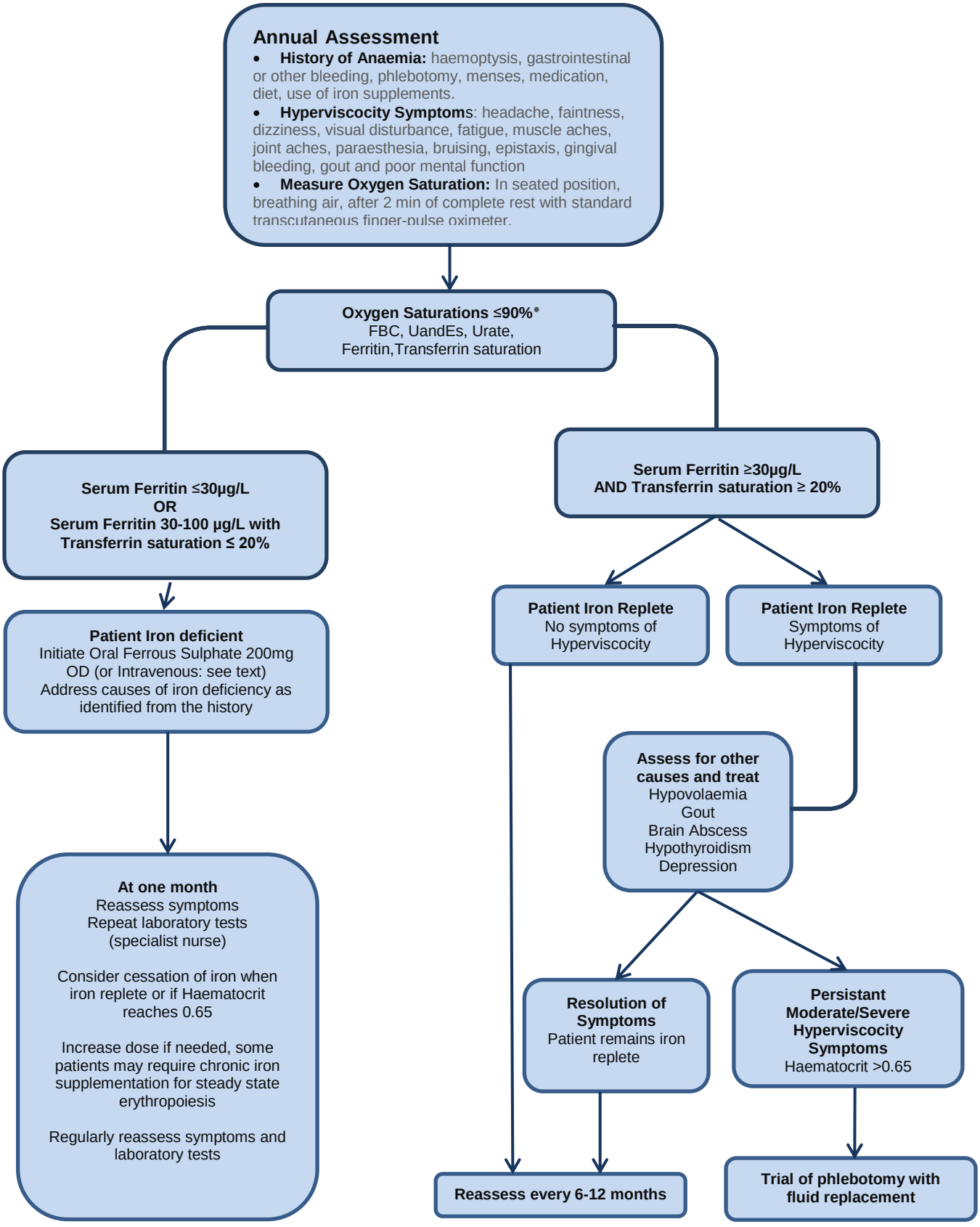

Figure 1 Flowchart for Investigation and Management of Iron Deficiency in Adult Congenital Heart Disease patients [* if differential peripheral cyanosis is suspected, saturation should be measured in toe, †If there is concomitant liver disease or other inflammation, serum ferritin may not reflect iron stores and transferrin saturation and transferrin should be performed, haematology advice regarding iron replacement and monitoring should be sought. ‡pulses of parenteral iron in patients who are intolerant of or who have failed oral iron therapy may be considered.] *Adapted from Spence MS et al. Lancet 2007 (13).*

Occasionally, haemoglobin levels may be appropriate or high (see Appendix for optimal levels of haemoglobin according to oxygen saturations) despite a serum ferritin ≤30µg/L. This may occur, for example, following iron therapy when iron stores are once again starting to deplete. Importantly, iron deficient patients still gain symptomatic benefit from iron supplementation, but should be monitored for signs and symptoms of hyperviscosity along with full blood count monitoring when initiated on iron supplementation. Gradual replacement of iron stores is advised to avoid excessive rebound of iron and resultant erythropoietic response, which may provoke hyperviscosity symptoms [13]. The objective is to provide sufficient iron to attain steady-state erythropoiesis as appropriate for the patient's underlying physiology.

Parenteral iron supplementation may be considered for patients where oral iron supplements are tolerated poorly, if there is insufficient oral absorption of iron, or the rate of loss exceeds the total absorption rate [14]. Particular care must be taken to avoid introducing air when administering IV iron; this may cause a paradoxical embolus in patients with right to left shunting. Parenteral iron preparations may cause hypersensitivity reactions (including anaphylaxis), even in patients who have received previous uneventful doses. Therefore careful monitoring for adverse effects is required (for at least 30 minutes following administration), as well as appropriate equipment for treating anaphylaxis.

If hyperviscosity symptoms (headache, faintness, dizziness, fatigue, tinnitus, blurred vision, peripheral paraesthesia, muscle pain and weakness) persist despite an adequate iron status, phlebotomy is exceptionally considered when haematocrit is > 65% and dehydration is absent [10,11,13]. In case of predominant headache symptoms, cerebral imaging is indicated to rule out cerebral abscesses.

4 Training, Implementation, Resource Implications

An overview of this guideline will be presented by the authors at the relevant departmental meetings (adult congenital heart disease, pulmonary hypertension, haematology). Presentations and awareness-raising sessions will be run for clinical teams – on request (by the adult congenital specialist nurses). Whilst it may be anticipated that there will be an increase in blood tests performed and iron therapy prescribed, the magnitude of this is small due to the limited population. Successful adoption of this guideline should defer prescription of other medications and further limit the increasingly out of favour practise of phlebotomy.

5 Monitoring Section

Periodically national and international guidance, as well as emerging evidence in the medical literature may influence changes in policy and procedural guidance. The authors will monitor these changes and ensure this policy reflects current requirements. The authors of this document and other members of the adult congenital multi-disciplinary team will monitor this policy on behalf of the Trust in relation to its effectiveness. It is recognised that 100% compliance with this guideline and its intended outcomes is unlikely as blood tests in cyanotic patients may sometimes be refused or inappropriate, nevertheless it is expected that provision of this information will improve current levels of adherence and where this is not met an action plan will be formulated and reviewed until completion. Please see the table below for standards and monitoring arrangements.

Standards	Monitoring and audit			
	Method	**By**	**Group**	**Frequency**
Case Review Audit	Ten sets of notes randomly selected will be audited annually to ensure that the Adult Congenital and Pulmonary Hypertension teams are compliant with the Newcastle Diagnosis and Management of Iron Deficiency in Adults with Cyanotic Congenital Heart Disease Guidelines	Adult Congenital Heart Disease Team	Congenital and Pulmonary Hypertension Teams	Three yearly
Cases for Concern	Cases for concern where morbidity or mortality arose in association with adherence to this guideline will be identified ad hoc and discussed	Adult Congenital Heart Disease Team	Congenital and Pulmonary Hypertension Teams	Monthly

The Adult Congenital Service will review the information and identify areas for improvement, develop remedial action plans and monitor these through to completion.

6 Evidence Review and Evaluation

The main body of this guideline has been based on the 2020 European Society of Cardiology clinical practice guidelines for the management of adult congenital heart disease with further reference to the corresponding 2018 American and 2010 Canadian guidelines for the management of adults with congenital heart disease [10,11,12]. Detail has been finalised following a thorough review of the medical literature as outlined in the references to this document.

7 References

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Appendix

The following table adapted from a paper by Broberg et al. [7] offers guidance on the optimal haemoglobin that may be expected for a given oxygen saturation. More simply *predicted haemoglobin = 61 – (O_2 saturations/2).*

Oxygen Saturation (%)	Predicted Haemoglobin (g/dl)	95% Confidence Intervals (g/dl)
93	16.1	14.4–17.9
90	17.5	16.0–19.0
87	18.8	17.5–20.1
85	19.7	18.4–21.0
83	20.6	19.2–21.9
80	21.9	20.4–23.4
77	23.2	21.4–25.0
75	24.1	22.1–26.1
73	25.0	22.8–27.3

The actual and optimal haemoglobin should be considered when making decisions about initiating iron therapy in the context of a low ferritin.