NHS SCOTLAND

SPAH
SCOTTISH PAEDIATRIC AND ADULT HAEMOGLOBINOPATHIES NETWORK

Use of Hydroxycarbamide in adults with Sickle Cell Disease

NOTE
This guideline is not intended to be construed or to serve as a standard of care. Standards of care are determined based on all clinical data available for an individual case and are subject to change as scientific knowledge and technology advance and patterns of care evolve. Adherence to guideline recommendations will not ensure a successful outcome in every case, nor should they be construed as including all proper methods of care or excluding other acceptable methods of care aimed at the same results. The ultimate judgement must be made by the appropriate healthcare professional(s) responsible for clinical decisions regarding a particular clinical procedure or treatment plan. This judgement should only be arrived at following discussion of the options with the patient, covering the diagnostic and treatment choices available. It is advised, however, that significant departures from the national guideline or any local guidelines derived from it should be fully documented in the patient's case notes at the time the relevant decision is taken.

Hydroxycarbamide (also known as Hydroxurea) is currently the only medication licensed in the UK for the prevention of painful crises in sickle cell disease. It has been shown in a large randomised-controlled study to decrease the frequency of painful vaso-occulusive crises and of chest crises in adults with homozygous sickle cell disease. It has more recently been shown in several studies to lessen the risk of other sickle-related complications and there is evidence to indicate a survival benefit.

Side effects include bone marrow suppression with the need for regular blood monitoring, gastro-intestinal disturbances, and increased skin and nail pigmentation. It is potentially teratogenic so contraception should be used whilst on the drug. It may affect male fertility and sperm storage should be discussed for males before commencement. There is no evidence of leukaemogenesis with long term follow-up of patients with sickle disease treated with hydroxycarbamide.

The main aim of therapy is to optimise HbF% without causing excess bone marrow suppression – achievement of maximum tolerated dose. Response should be decided clinically however, as some patients who fail to get an increase in HbF% seem to benefit clinically.

Indications for use in adults[1].
It is good practice to discuss the benefits and risks of hydroxycarbamide **with all patients with sickle cell disease (HbSS/Sβ^0) regardless of the severity** of their condition. This is because of the associated reduction in mortality. **(Grade 1B evidence)**

Patients with moderate or severe sickle cell disease (HbSS/Sβ$^{0)}$ should be offered hydroxycarbamide therapy:

- 3 or more episodes of moderate or severe painful crises in a 12 month period (Grade 1A evidence)
- Sickle cell pain that interferes with daily activities and quality of life (Grade 1C evidence)
- 1 or more life threatening complications of the disease, such as acute chest syndrome (Grade 1A evidence)
- second line therapy for secondary stroke prevention when transfusions are contraindicated or unavailable (Grade 1B evidence)
- Sickle nephropathy with persisting proteinuria despite angiotensin-converting-enzyme inhibitor/angiotensin receptor blocker therapy, consider the addition of hydroxycarbamide therapy (Grade 2C evidence)
- recurrent priapism (Grade 2D evidence)
- Chronic hypoxia (Grade 2C evidence)
- Symptomatic chronic anaemia (Grade 1C evidence)

Other indications (such as pulmonary hypertension, AVN) and the use of hydroxycarbamide in other genotypes e.g. HbSC should be discussed with consultant colleagues within the network.

Cautions and Contraindications

- Pregnancy
- Not practicing active contraception (if sexually active)
- Active hepatitis
- Hb<60g/l – discuss at MDT
- Neut<1x10^9/l, Plts<100x10^9/l – discuss at MDT
- eGFR < 30 ml/min/1·73 m^2

Requirements prior to starting therapy

- The benefits and hazards of using hydroxycarbamide should be considered for each patient individually, and discussed
- Ensure that the patient is willing to attend regularly to monitor blood counts
- Discuss the unknown effects on fertility with male patients. Offer sperm banking.
- It is important to discuss the risks of Hydroxycarbamide in pregnancy and recommend contraception whilst on the drug.

Baseline investigations

- FBC and reticulocytes
- HbF%
- U+Es, LFTs, Urate, LDH

Regimen details:

- Commence at 15mg/kg/day orally rounded to nearest 500mg
- 5–10 mg/kg/day starting dose if the patient has chronic kidney disease (eGFR < 60 ml/min/1·73 $m^{2)}$. Not recommended if eGFR < 30 ml/min/1·73 m^2.
- The dose can be escalated by 5 mg/kg/day every 8–12 weeks, aiming for a neutrophil count of 2–3 × 10^9/l and stopping if neutrophils fall below 1 × 10^9/l or if there is other haematological toxicity or until maximum dose of 35mg/kg/day. This is the maximum tolerated dose.
- An optimal clinical and laboratory response to treatment with hydroxycarbamide may take 12 months

Monitoring

- FBC and retics after 2 weeks initially or after any dose change
- FBC and retics 2-3 monthly when counts stable
- 2-3 monthly U+Es, LFTs, Urate, LDH and HBF%

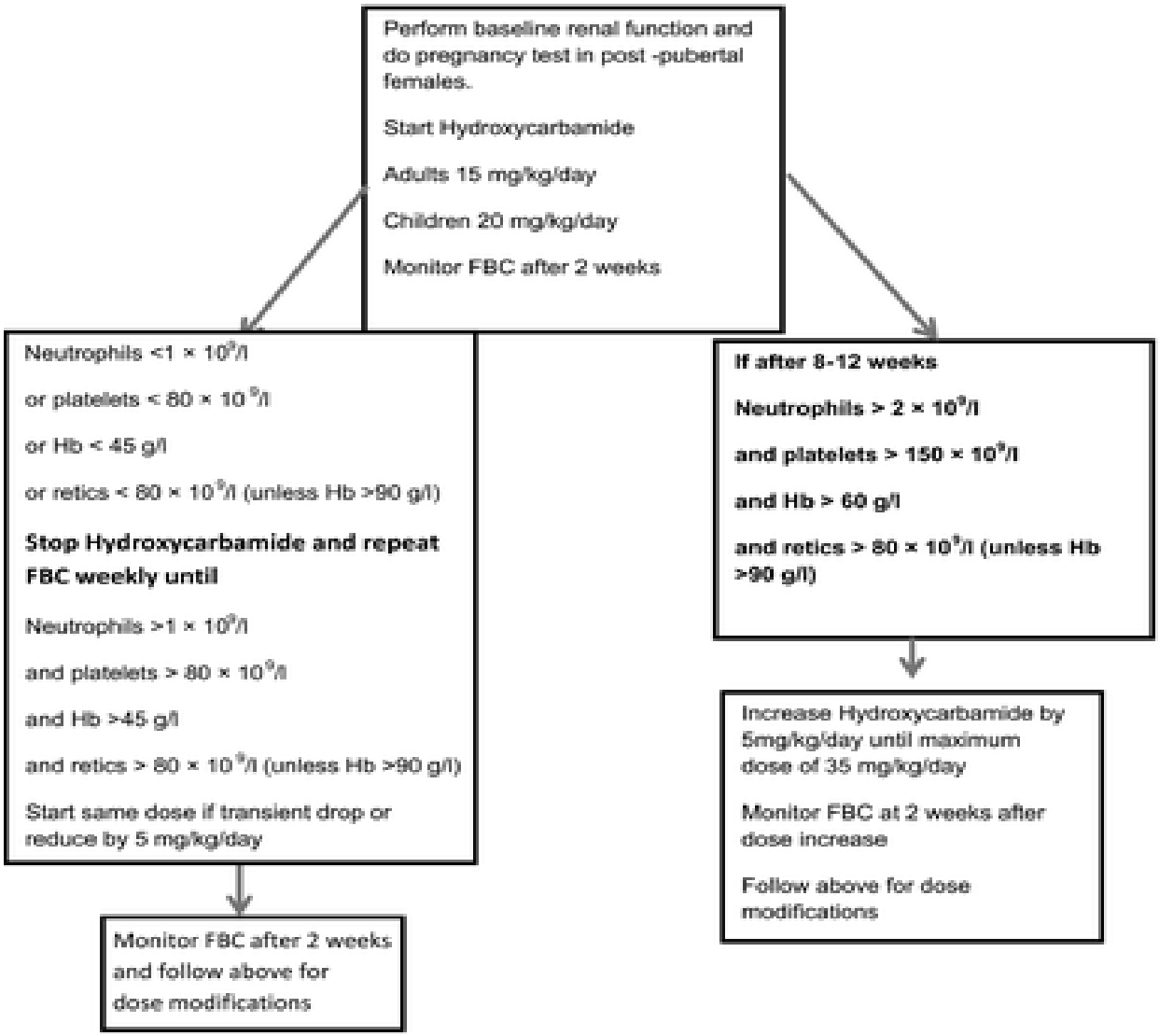
Toxicity

Stop hydroxycarbamide when results reach parameters below (unless experienced user and strong indication to continue at a reduced dose rather than stopping altogether)

- Neutrophils < 1.0 x 10^9/l
- Platelets < 80 x 10^9/l
- Reticulocytes < 80 x 10^9/l (unless Hb >90g/l)
- Haemoglobin <45 g/l or 30g/l from baseline
- When FBC recovered restart at 5mg/kg/day (or 1 capsule – 500mg) lower. This is the maximum tolerated dose (MTD)

Figure 1

Algorithm for hydroxycarbamide dosing and monitoring (From BCSH guideline)



- Once a stable dose is established, laboratory safety monitoring should include FBC and reticulocyte count every 2-3 months. Follow above algorithm for dose modifications. HbF and MCV can be used to monitor effect/compliance

Caution

- if there is a significant rise in Hb (>110g/l in HbSS) review the hydroxycarbamide dose and consider venesection
- if there is a downwards trend in FBC parameters, increase frequency of monitoring
- use with caution in renal impairment: start at a lower dose and increment more cautiously. Not recommended if eGFR < 30 ml/min/1·73 m^2.
- Hydroxycarbamide therapy should be continued during hospitalizations or illness unless due to febrile neutropenia or bleeding with thrombocytopenia
- patients should be informed to present to hospital if unwell with high fevers and infection and inform hospital staff to perform a FBC in case of neutropenia.

Preconception and Pregnancy

- Hydroxycarbamide is considered teratogenic in mice at suprapharmocological doses. Data in human pregnancy with hydroxycarbamide at therapeutic levels is limited, and for this reason it is recommended that contraception is used whilst on hydroxycarbamide, and it is stopped in advance of trying for pregnancy.
- although it is not advised, if a patient/patient's partner becomes pregnant whilst using hydroxycarbamide then individual discussion about risks of continuing pregnancy and detailed 20week scan are advised.
- prenatally and during pregnancy, consider a transfusion programme if there is a severe clinical phenotype as an alternative to hydroxycarbamide treatment.

Toxicities

Common:	Bone marrow suppression and cytopenias Nausea and vomiting Diarrhoea Skin rash Mouth ulcers
Uncommon:	Alopecia Leg ulcers Hyperpigmentation of nails and skin
Other:	Unclear effect on sperm count and function hence cryopreservation may be offered No evidence of increased leukaemogenesis in patients with sickle cell disease

Definition of failure to respond to hydroxycarbamide

- a failure to respond to hydroxycarbamide can be classified as failure to improve frequency and severity of painful episodes or ACS. Failure of response should be based on clinical criteria rather than laboratory data, as benefit can be seen even at a low HbF%.
- a significant proportion of failure to respond to hydroxycarbamide is due to non-adherence/compliance or failure to escalate to the maximum tolerated dose.
- an optimal clinical and laboratory response to treatment with hydroxycarbamide may take 12 months. Therefore, a 6-month trial on the maximum tolerated dose is required prior to considering discontinuation due to treatment failure, whether due to lack of adherence or failure to respond to therapy.
- for the patient who has a clinical response, long-term hydroxycarbamide therapy is indicated.

1. British Society for Haematology: Guidelines for the use of hydroxycarbamide in children and adults with sickle cell disease https://doi.org/10.1111/bjh.15235